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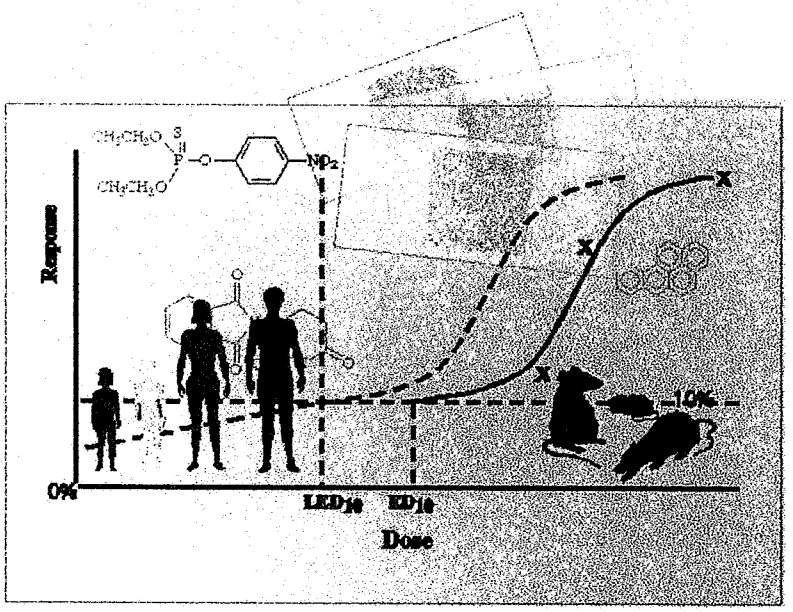
MAN HEALTH RISK ASSESSMENT

TERBUFOS



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

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HUMAN HEALTH RISK ASSESSMENT

TERBUFOS

PHASE 5

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Introduction

This revised human health risk assessment for terbufos incorporates the comments received from the U.S. Department of Agriculture, several new studies generated by American Cyanamid, and the most recent risk assessment techniques and policies. The hazard component of the risk has been reassessed in light of recently-submitted oral acute and subchronic rat neurotoxicity studies, and rat dermal toxicity studies conducted on the two granular end-use products. Probabilistic reassessment of acute dietary risks has been conducted using the DEEM™ Software, recent banana and corn field trial data, revised usage (percent crop treated) data, the hazard endpoint and dose derived from the recent rat neurotoxicity study, and the reduced FQPA Safety Factor. Chronic dietary risks were revised using DEEM™, the recent residue data, new usage data, the reduced FQPA factor, and, as in previous assessments, the endpoint and dose selected from the 1-year and 28-day cocritical oral dog toxicity studies. Occupational risks were recalculated using new chemical- and formulation-specific worker exposure studies as well as hazard endpoints and doses derived from the new route- and formulation-specific rat dermal toxicity studies. Residential exposures are not expected. A qualitative assessment of the potential exposure to terbufos through drinking water was conducted. Aggregate acute and chronic risks resulting from exposure to terbufos via food and drinking water were assessed.

Executive Summary

Background

The Health Effects Division (HED) of EPA's Office of Pesticide Programs has evaluated the terbufos database and conducted a revised human health risk assessment for terbufos. This assessment supersedes the 4/6/98 preliminary risk assessment (made publicly available) and the 3/4/99 assessment, which incorporated the public comments received on the 4/6/98 assessment.

Uses

Terbufos [S-[(tert-butylthio)methyl] O,O-diethyl phosphorodithioate] is an organophosphate insecticide/nematicide registered in the United States for preplant, at-plant, and early postemergence use on corn, sorghum, and sugar beets. It is also used on bananas in Central and South America; applications may be within several days of harvest. There are six cholinesterase-inhibiting residues of toxicological concern, all of which are included in the tolerance expression at 40 CFR 180.352; these are terbufos, terbufos sulfoxide, terbufos sulfone, terbufos O-analog, terbufos O-analog sulfoxide, and terbufos O-analog sulfone. Terbufos is generally applied using ground equipment and is always soil-incorporated. There are two registered end-use products, the 15% granular (15G) and the 20% polymeric granular (20CR). No residential exposure to terbufos is expected.

Toxicity

As with other organophosphates, the principal toxic effects induced by terbufos are related to its cholinesterase-inhibiting (ChE) activity. Terbufos is one of the more potent cholinesterase inhibitors, having No Observed Adverse Effect Levels (NOAELs) of 0.15 mg/kg/day in an acute rat oral neurotoxicity study and 0.005 mg/kg/day in a 28-day oral dog study. The respective Lowest Observed Adverse Effect Levels (LOAELs) were 0.30 mg/kg/day (plasma ChE inhibition and clinical signs) and 0.015 mg/kg/day (plasma ChE inhibition). Upon applying the appropriate uncertainty factors, the derived Reference Doses (RfDs) used in risk assessment are 0.0003 mg/kg/day for acute dietary and 0.00005 mg/kg/day for chronic dietary assessments. **It is the very low numerical value (high toxicity) of the hazard components of the risk that is driving the dietary assessments.** Similarly, a very low NOAEL of 0.00001 mg/L (0.0035 mg/kg/day) was observed in a 21-day rat inhalation study in which brain, plasma, and red blood cell (RBC) ChE inhibition was observed at the LOAEL of 0.00004 mg/L. **Again, the high toxicity of terbufos via the inhalation route is driving the occupational risk assessments.** In the case of the dermal route of occupational exposure, the hazard components were selected from two 28-day dermal toxicity studies in which rats were exposed to the two granular end-use products.

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NOAELs from these studies were 0.32 mg/kg/day for assessment of dermal risk involving the 15G formulation and 2.0 mg/kg/day in the case of the 20CR. There was no evidence of terbufos-induced carcinogenicity. There were no developmental toxicity, no increased sensitivity of offspring, and no neuropathological effects associated with terbufos.

FQPA Safety Factor

The Food Quality Protection Act (FQPA) of 8/3/96 requires that a 10-fold safety factor be applied to risk assessments to protect against the potential increased sensitivity of infants and children. In the case of terbufos, hazard and exposure considerations led to the conclusion that this factor should be removed (reduced to 1X) rendering the acute and chronic RfDs equivalent to the respective Population Adjusted Doses (PADs) which are derived by dividing the RfD by the FQPA Safety Factor.

Dietary Risk

Dietary risk assessments reflected highly refined exposure estimates; anticipated residues and percent-crop-treated figures were incorporated. Refinements permit more realistic food exposure estimates for comparison of Drinking Water Levels of Comparison (DWLOC) with estimates of potential drinking water concentrations provided by the Environmental Fate and Effects Division (EFED). A probabilistic/Monte Carlo type of acute dietary risk assessment was conducted using an acute PAD (aPAD) of 0.0003 mg/kg/day; **acute risks to all population subgroups were ≤86% of the aPAD.** Chronic risks were calculated using a chronic PAD (cPAD) of 0.00005 mg/kg/day; **chronic dietary risks to all population subgroups were ≤9% of the cPAD.**

Water Risk

The EFED water assessment included modeling in groundwater and surface water of terbufos separately as well as combined with terbufos sulfoxide and sulfone, the major residues of toxicological concern encountered in the soil/water column. Estimated Environmental Concentrations (EECs) were compared to DWLOCs: in many scenarios, the EECs for combined residues exceeded the DWLOCs for both acute and chronic water consumption by both adults and children. Also, modeled terbufos exposure estimates due to drinking water alone (i.e., without considering food sources) suggest potential concern for adults and children from exposure to terbufos in drinking water.

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Aggregate Risk

Aggregate exposure is comprised solely of food and water sources as there is no residential exposure to terbufos. Acute and chronic dietary (food only) assessments result in risks that are beneath the Agency's level of concern. **However, based on modeling, there is potential concern for terbufos residues in drinking water.** Water monitoring data would permit refinement as well as quantitative inclusion of dietary exposure via water in aggregate risk calculations.

Occupationa Risk

Occupational risk assessments included chemical-specific and formulation-specific worker exposure data as well as route-specific and formulation-specific hazard endpoints/doses. As a result, both separate and combined dermal and inhalation Margins of Exposure (MOEs) were calculated. Occupational risks to handlers are below the Agency's level of concern (MOEs >100) for both the 15G and 20CR formulations when closed loading and closed cabs are used and when the 20CR is applied using closed loading and open cab. Some scenarios have associated risks above the level of concern when the 20CR is applied via open cab and open loading. Note that the 15G is not marketed in bags (only available in "Lock-N-Load"). No postapplication exposure is expected based on the terbufos use pattern.

Database Requirements

The terbufos database is complete and adequate for the conduct of this revised human health risk assessment. However, confirmatory neurotoxic esterase (NTE) data on the hen are required to support the hen delayed neurotoxicity study (OPPTS 870.6100).

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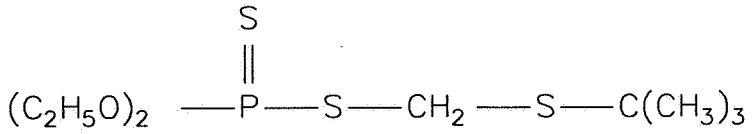
I. Physical/Chemical Properties

Terbufos [S-[(tert-butylthio)methyl] O,O-diethyl phosphorodithioate] is an organophosphate insecticide/nematicide registered in the United States for preplant, at-plant, and early postemergence use on corn, sorghum, and sugar beets.



Other identifying characteristics and codes are:

Empirical Formula: $C_9H_{21}O_2PS_3$
Molecular Weight: 288.4
CAS Registry No.: 13071-79-9
Shaughnessy No.: 105001

Technical terbufos is a colorless to pale yellow clear liquid with a mercaptan-like odor, a boiling point of 55 °C at 0.02 mmHg, and a density of 1.11 g/ml at 20 °C. The solubility of terbufos in water at 25 °C is 5.4 ppm and its solubility in acetone, acetonitrile, benzene, chloroform, dichloromethane, ethanol, n-heptane, methylene chloride, and toluene is reported as ≥ 100 g/100 ml at 20 °C. Water solubilities of the two major soil/water degradates are 3214 and 407 mg/L for terbufos sulfoxide and terbufos sulfone, respectively, at 25 C (C. Swartz, 11/19/98, D250379 and D250390).

II. Hazard Assessment

The toxicology database of terbufos was reviewed by L. Taylor (8/26/99, D258987). Terbufos is a cholinesterase inhibitor, and it produces the associated clinical signs, such as tremors, unsteady gait, decreased activity, salivation, muscle weakness, and disturbed balance in rats, dogs, and mice. Decreased cholinesterase activity [RBC, plasma, brain] was observed in rats, dogs, rabbits, and mice following acute, subchronic, and chronic exposure *via* the oral, dermal, and inhalation routes of exposure.

Terbufos is highly acutely toxic via the oral, dermal, and inhalation routes of exposure. Males appear to be more sensitive to the toxic and lethal effects of terbufos than females via the oral and dermal routes, and females appeared more sensitive via the inhalation route. Dermal and eye irritation studies resulted in deaths, and the dermal sensitization study was waived due to lethality. In the absence of dermal absorption data, dermal absorption is considered to be 100% [default value]; there is evidence that terbufos toxicity via the dermal route approaches that via the oral route provided there is sufficient dermal contact. Note that, in the case of terbufos, dermal toxicity studies served as the sources of dose and endpoints for dermal risk assessment purposes.

Terbufos did not cause acute delayed neurotoxicity in hens, and there was no evidence of neuropathology in the acute, subchronic, and chronic studies in rats, the subchronic and chronic studies in dogs, or the mouse long-term study. In the acute neurotoxicity study in rats, no effects were observed on motor activity, but several functional observational battery [FOB] parameters were affected [ataxia, decreased forelimb grip strength, tremors]. No treatment-related effects were observed on motor activity or in the FOB parameters measured in the subchronic neurotoxicity study in rats.

Terbufos did not produce developmental toxicity, and there was no evidence of malformations or decreases in the number of pups and/or litters or surviving offspring. There is no indication of an increased sensitivity of offspring in rats or rabbits after prenatal and/or postnatal exposure. Reduced male fertility was observed in the 2-generation reproduction study in rats.

Terbufos is not carcinogenic and is classified as a Group E chemical, indicating that it is "Not Likely" to be carcinogenic in humans via relevant routes of exposure. This classification is based on adequate studies in two animal species. No evidence of mutagenicity was seen in any study.

Following oral administration, terbufos is rapidly and extensively absorbed in the gastrointestinal tract, metabolized, and the metabolites [not parent compound] are rapidly excreted, mainly via the urine, within the first 24 hours after dosing. There is no

evidence of bioaccumulation. The predominant radiolabeled compound found in the feces was terbufos. Neither terbufos nor its metabolites accumulated in any tissue to any extent, but the highest level of radiolabel was found in the lungs. The percent of the administered dose detected in the urine [168 hours] ranged from 69.3% to 86.3%, in feces ranged from 5.4% to 17.4%, and in expired air ranged from 2.6% to 4.2%. No sex differences were observed. Following repeat exposure, there appeared to be a shift towards greater urinary elimination. The proposed metabolism of terbufos is via desulfuration and/or sulfoxidation, followed by hydrolysis of the phosphorus-sulfur bond and exzymatic S-methylation.

For details of the terbufos hazard assessment, refer to the Terbufos Toxicology Chapter of the Reregistration Eligibility Decision by L. Taylor (D258987; 8/26/99).

A. Dose Response and Hazard Endpoint Selection

A summary of the terbufos toxicology studies and hazard dose and endpoint selections made by the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) is provided in the HIARC report by L. Taylor dated 8/30/99. Table 1 contains the acute toxicity endpoints which are especially important for labeling purposes, eg. for label warnings and the level of personal protective equipment (PPE) necessary for terbufos handlers. Table 2 contains a summary of the hazard doses and endpoints selected for use in the various human health risk assessments. Table 1 summarizes the results of acute toxicity studies on terbufos.

Table 1. Acute Toxicity of Terbufos

Guideline No.	Study Type	Results	Toxicity Category
870.1100/§81-1	Acute Oral - rat	LD_{50} = 1.4 [females] mg/kg	I
870.1200/§81-2	Acute Dermal - rabbit	LD_{50} = 0.87 mg/kg	I
870.1300/§81-3	Acute Inhalation - rat	LC_{50} = 1.7 µg/L	I
870.2400/§81-4	Primary Eye Irritation	all rabbits died	I*
870.2500/§81-5	Primary Skin Irritation	all rabbits died	I*
870.2600/§81-6	Dermal Sensitization	waived due to lethality	N/A
870.6100/§81-7	Delayed Neurotoxicity	not a delayed neurotoxicant	N/A
870.6200/§81-8	Acute Neurotoxicity	NOAEL = 0.15 mg/kg; LOAEL = 0.30 mg/kg, based on findings in FOB and ChEI	N/A

*Assumed (could not be determined) due to lethality.

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Toxicological endpoints for risk assessments with terbufos are tabulated below:

Table 2. Summary of Toxicology Endpoint Selection

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	NOAEL= 0.15 UF = 500	Plasma ChE inhibition in both sexes	Acute Oral Neurotoxicity in Rats
		Acute RfD = 0.0003 mg/kg	
Chronic Dietary	NOAEL=0.005 UF = 100	Plasma ChE Inhibition in both male and female dogs	Chronic/28-day Toxicity -Dog
		Chronic RfD = 0.00005 mg/kg/day	
Short- and Intermediate-Term (Dermal) ***20 CR only***	NOAEL= 2*	plasma, RBC, brain ChE Inhibition observed at higher doses in range-finding study	28-Day Dermal Study on 20CR formulation in Female Rats
Short- and Intermediate-Term (Dermal) ***15G only***	NOAEL = 0.32*	Plasma and brain ChE Inhibition	28-Day Dermal Study on 15G formulation in Rats
Long-Term Dermal	This risk assessment is not required (long-term dermal exposure to terbufos is not expected).		
Short- and Intermediate-Term [Inhalation]	NOAEL= 0.00001 mg/L*	Plasma , RBC, brain ChE Inhibition	Subchronic Inhalation Study in Rats
Long-Term Inhalation	This risk assessment is not required (long-term inhalation exposure to terbufos is not expected).		

*MOE for worker exposure risk assessments = 100; no registered residential uses

B. FQPA Safety Factor

The FQPA Safety Factor Committee met on July 26, 1999 to reevaluate the hazard and exposure data for terbufos as bases for making a recommendation on the magnitude of the FQPA Safety Factor (as required by FQPA). The FQPA safety factor recommendation in the July 26, 1999 report supersedes that previously reported for terbufos in the *FQPA SAFETY FACTOR RECOMMENDATIONS FOR THE ORGANOPHOSPHATES* dated August 6, 1998. At that time, the FQPA safety factor recommendation was 3X due to the data gaps for the acute and subchronic neurotoxicity studies.

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These data requirements have since been satisfied and, therefore, the Committee recommended that the FQPA safety factor be **removed (1X)** for terbufos. The rationale for removal (reduction to 1X) of the FQPA Safety Factor is:

- ❑ The toxicology database is now complete (previous data gaps have been satisfied);

- ❑ There is no indication of increased susceptibility of young rats or rabbits to terbufos. In the developmental and reproduction toxicity studies, effects in the fetuses/offspring were observed only at or above treatment levels that resulted in evidence of parental toxicity;

- ❑ The HIARC determined that a developmental neurotoxicity study in rats is not required;

- ❑ The dietary food exposure assessment does not underestimate the potential exposure to infants and children from residues in food;

- ❑ The dietary water exposure assessment should include worst-case assumptions in modeling the degradates of concern (terbufos sulfone and sulfoxide) so that the drinking water risk assessments do not underestimate exposure from the cholinesterase-inhibiting metabolites; and

- ❑ No exposure is expected to infants and children from residential (non-occupational) sources.

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III. Dietary Exposure and Risk Assessment

A. Food Sources of Dietary Exposure

Existing and reassessed tolerances are established for the combined residues of terbufos and its cholinesterase-inhibiting metabolites in or on plant commodities [40 CFR §180.352(a)]. The phosphorylated (cholinesterase-inhibiting) metabolites include terbufos oxygen analog (oxon); terbufos sulfoxide; terbufos sulfone; terbufos oxygen analog sulfoxide; and terbufos oxygen analog sulfone. Adequate data collection and enforcement methods are available to detect terbufos residues in plant commodities. No food/feed additive, meat, milk, poultry, or egg tolerances have been established for terbufos. Tolerances are not required for residues in livestock commodities, since HED has concluded there is no reasonable expectation of finite residues [40 CFR §180.6(a)3].

No new residue data have been generated for the current analyses. The registrant submitted a sensitivity analysis for acute dietary exposure and risk [AMCY submission dated 5/21/99 (MRID No. 44834301)], which discusses hazard inputs to the analysis, USDA consumption data, and all available residue data for relevant commodities. The registrant proposes that HED consider removing 4 banana field trial residue values from terbufos dietary exposure analyses. The sensitivity analysis demonstrated that estimated acute dietary exposure and risk can largely be attributed to the weighting of older (1983 and 1987) banana residue data generated in Costa Rica at the 1X rate of 3 g ai/mat. The registrant's analyses included only the more recent (1997) studies conducted in Honduras and Mexico at the 1X rate of 4 g ai/mat (and assuming zero residue values for residues less than the LOD) resulted in much lower estimated acute dietary exposure and risk. In support of these assumptions and lower dietary exposure estimates, the registrant cited PDP and FDA monitoring data in which terbufos, terbufos sulfone and terbufos oxygen analog sulfone residues were below the limit of detection in bananas.

The registrant's sensitivity analysis serves to further characterize acute dietary exposure; however, no changes were made to the revised HED assessment (C. Swartz memo dated 8/26/99) on the basis of the sensitivity analysis for the following reasons: (i) revised acute dietary risk estimates were below HED's level of concern; (ii) PDP and FDA monitoring data did not measure all terbufos residues of concern; (iii) all banana residue data were included to achieve adequate geographic representation for banana imports; (iv) total terbufos residues between the LOD and the LOQ were observed in the more recent studies, indicating the presence of finite residues; and (v) the registrant did not provide compelling reasons to exclude the 1983 and 1987 banana field trial data. The submission is currently under review (C. Swartz, 9/99). For the current analyses, there are no changes in the residue inputs from field trial data.

The chronic anticipated residues used in previous analyses have been used in the current revised analysis along with the weighted average %CT estimates (rather than the estimated maximum %CT). In previous HED acute dietary exposure analyses, banana and sweet corn RDFs submitted by AMCY were used. HED policies for conducting acute probabilistic analyses have been modified since the 2/99 terbufos dietary exposure analysis (memo, M. Stasikowski, 8/20/99); however, the changes do not affect the terbufos residue inputs, which were derived from field trials. Therefore, residue inputs from the previous analyses have been used in the current analyses, with minor changes to reflect the new estimated maximum %CT estimates.

Revised acute probabilistic and chronic dietary exposure estimates have been generated (C. Swartz, 8/26/99, D258668) to account for **removal (reduction to 1X) of the safety factor** in accordance with FQPA. Also, a revised chronic dietary exposure and risk assessment was necessary to reflect the current HED policy which allows for use of the **weighted average of percent crop treated (%CT)**, rather than the estimated maximum, in chronic dietary exposure assessments. The dose and endpoint from the acute oral rat neurotoxicity study (Table 2) used in the current assessment had already been used for acute dietary risk assessment in the interim (W. Hazel, D253850) human health risk assessment dated 3/4/99.

The terbufos dietary exposure analyses are based largely on residues below the limit of detection (LOD), between the LOD and the limit of quantitation (LOQ), or at or just above the LOQ. Available monitoring data did not include all terbufos residues of concern, but qualitatively support the results of the dietary exposure analyses conducted using field trial data.

HED conducts dietary risk assessments using the Dietary Exposure Evaluation Model (DEEM™), which incorporates consumption data generated in USDA's Continuing Surveys of Food Intakes by Individuals (CSFII), 1989-1992. For chronic dietary risk assessments, the three-day average of consumption for each sub-population is combined with residues in commodities to determine average exposure in mg/kg/day. For refined acute dietary risk assessments, the entire distribution of consumption events for individuals is multiplied by a distribution of residues (probabilistic analysis, referred to as "Monte Carlo," risk at 99.9th percentile of exposure reported) to obtain a distribution of exposures in mg/kg/day.

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Estimated chronic dietary exposure and risk for terbufos are significantly below HED's level of concern. The most highly exposed population subgroup is non-nursing infants, with an estimated exposure corresponding to 9% of the cPAD. Estimated dietary exposure to the general U.S. population is lower, corresponding to 2% cPAD (Table 3).

In the acute dietary exposure assessment, risk at the 99.9th percentile of exposure is reported since the probabilistic analysis was refined using residue distribution files and %CT data. **Estimated acute dietary exposure and risk are below HED's level of concern for terbufos.** At the 99.9th percentile of exposure, the most highly exposed population subgroup is non-nursing infants, with 86% of the aPAD consumed. Estimated dietary exposure to the general U.S. population is much lower, corresponding to 23% aPAD (Table 3).

Additional analyses conducted to further characterize terbufos acute dietary risk indicate that bananas are the most significant contributor to estimated risk. When bananas are excluded from the analysis, the most highly exposed population subgroup is children 1-6 years, with an exposure corresponding to 12% aPAD. Very little effect on the risk results upon exclusion of sweet corn or field corn from the analysis (Table 3).

The chronic and acute analyses do not take into consideration the potential for reduction of terbufos residues in cooked/canned/processed bananas and sweet corn, since there are no chemical-specific cooking studies. HED will refine the terbufos dietary exposure analyses if such data become available.

Table 3. Terbufos Acute Probabilistic (Monte Carlo) and Chronic Dietary Exposure and Risk Estimates.[1]

Population Subgroup	Chronic Assessment		Acute Assessment 1 (99.9th %-ile)		Acute Assessment 2 (99.9th %-ile)		Acute Assessment 3 (99.9th %-ile)		Acute Assessment 4 (99.9th %-ile)	
	Exposure mg/kg/day	%cPAD	Exposure mg/kg/day	%aPAD	Exposure mg/kg/day	%aPAD	Exposure mg/kg/day	%aPAD	Exposure mg/kg/day	%aPAD
General US Population	0.000001	2	0.000069	23	0.000017	6	0.000063	21	0.000070	23
All infants (<1 yr)	0.000004	7	0.000246	82	0.000006	2	0.0000254	82	0.000253	82
Nursing infants	0.000001	3	0.000129	43	0.000002	<1	0.000128	43	0.000125	42
Non-nursing infants	0.000005	9	0.000259	86	0.000006	2	0.000260	86	0.000260	86
Children 1-6 yrs	0.000002	5	0.000137	46	0.000039	13	0.000133	44	0.000141	46
Children 7-12 yrs	0.000001	3	0.000068	23	0.000026	9	0.000063	21	0.000069	23
Females 13-19	0.000001	1	0.000035	12	0.000012	4	0.000032	11	0.000036	12
Females 20+	0.000001	1	0.000036	12	0.000012	4	0.000034	11	0.000037	12
Females 13-50	0.000001	1	0.000036	12	0.000012	4	0.000033	11	0.000036	12
Males 13-19	0.000001	2	0.000046	16	0.000016	5	0.000041	14	0.000050	16
Males 20+	0.000001	1	0.000029	10	0.000012	4	0.000028	9	0.000032	10
Assessment Description	Includes All Commodities		Includes All Commodities		Excludes Bananas		Excludes Sweet Corn		Excludes Field Corn	

[1]The chronic Population Adjusted Dose (cPAD) is 0.00005 mg/kg/day. The acute Population Adjusted Dose (aPAD) is 0.0003 mg/kg/day.

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B. Drinking Water Sources of Dietary Exposure

EFED has updated the environmental fate information, reviewed the available monitoring data for parent terbufos in both surface and ground water, and performed additional modeling of parent terbufos and its primary oxidative metabolites of toxicological concern (terbufos sulfoxide and sulfone) in surface water and ground water (J. Breithaupt, 8/26/99). EFED has considered recent data on the abiotic hydrolysis of parent terbufos and the oxidative metabolites terbufos sulfoxide and sulfone as well as aerobic aquatic metabolism data for the above compounds in aerobic natural pond water. The abiotic hydrolysis data were not used in surface water modeling because the aerobic aquatic metabolism data are more relevant. For ground water, the hydrolysis data provide useful information on the persistence and degradation products if terbufos residues were to reach ground water. The newer PRZM model has more soil incorporation options than the older PRZM model; use of these options resulted in significant changes in the EECs. In general, available monitoring data are not useful to determine the potential for terbufos to reach groundwater because the metabolites were not measured. For both surface water and groundwater, the sum of terbufos and its two principal oxidative metabolites should be used for dietary risk assessment purposes although terbufos alone is presented in Table 4 for comparative purposes.

For all three labeled crops the model results suggest negligible surface water residues for application procedures other than T-band application. However, EFED is concerned that incorporation options in the most recent PRZM version may not adequately represent the availability of the chemical for runoff. The Agency has received reports of aquatic incidents for corn, for all application procedures including in-furrow application. EFED believes that in-furrow application can be associated with significant runoff for any of the three labeled crops. While EFED believes that application procedures can have a large influence on runoff, they do not have field information confirming differences as dramatic as those suggested by the model results for terbufos.

1. Groundwater

The SCI-GROW model (Screening Concentrations in Ground Water) is a model for estimating "upper bound" concentrations of pesticides in ground water. SCI-GROW provides a screening concentration; an estimate of likely ground water concentrations if the pesticide is used at the maximum allowed label rate in areas with ground water vulnerable to contamination. In most cases, a majority of the pesticide use area will have ground water that is less vulnerable to contamination than the areas used to derive the SCI-GROW estimate.

The SCI-GROW model is based on scaled ground water concentrations from ground water monitoring studies, environmental fate properties (aerobic soil half-lives and organic carbon partitioning coefficients-K_{oc}'s) and application rates. The SCI-GROW model does not make use of information on application procedures. The residues of parent terbufos, terbufos sulfoxide, and terbufos sulfone in the aerobic soil metabolism study (MRID 00156853) were added for each sampling interval, and the half-life was calculated by linear regression of the log of the summed concentration against time. Refer to Table 4 for terbufos groundwater EECs for dietary risk assessment purposes.

2. Surface Water

Tier II surface water EECs were generated using PRZM 3.12 and EXAMS 2.975 using decline of parent terbufos and formation and decline of the sulfoxide and sulfone metabolites in a sequential degradation pattern in both the field and the pond. EECs are presented in Table 4 for total parent + sulfoxide + sulfone. Terbufos per se is a major residue near application but within several days, the oxidative metabolites are the principal residues in both surface and drinking water. The two metabolites are the only residues that are likely to be found in the environment except very soon after application. The scenarios modeled included application to field corn in Ohio, grain sorghum in Kansas, and sugar beets in Minnesota. EFED also used a recently-approved label that reduces the maximum rate for knifed-in applications of terbufos for sugar beets and grain sorghum from 3.9 lb ai/A to 2 lb ai/A. EFED has also calculated EECs in surface water for total toxic residues of those Terbufos residues that are observed in environmental fate studies (parent, terbufos sulfoxide and sulfone). A Tier II EEC for a particular crop or use is based on a single site that represents a high exposure scenario for the crop or use. Weather and agricultural practices are simulated at the site for 36 years to estimate the probability of exceeding a given concentration (maximum concentration or average concentration) in a single year. Maximum EECs are calculated so that there is a 10% probability that the maximum concentration in a given year will exceed the EEC at the site; 4-day, 21-day, 60-day, and 90-day average EECs are calculated so that there is a 10% probability that the maximum average concentration for a given duration (4-day, 21-day, etc.) will equal or exceed the EEC at the site. This can also be expressed as an expectation that water concentrations will exceed EECs once every 10 years. EECs are presented in Table 4.

3. Acute and Chronic DWLOCs

Drinking Water Levels of Comparison (DWLOCs) represent the maximum contribution to the human diet that may be attributed to residues of a pesticide in drinking water after dietary exposure and, in the case of chronic assessments, residential exposure are subtracted from the aPAD or cPAD. In the case of terbufos, there is no residential exposure. Acute and chronic DWLOCs for terbufos were calculated using anticipated residues in food. These are presented in Table 5. Comparisons are made between DWLOCs and the estimated concentrations of terbufos plus its sulfoxide and sulfone in surface water and ground water generated via PRZM/EXAMS and SCI-GROW, respectively. Refer to Table 3 for food residue exposure values (in mg/kg/day) and to Table 4 for the full range of EECs.

Table 4. EECs of Terbufos + Metabolites in Surface Water and Groundwater to be Used for Comparison to Acute and Chronic Risk DWLOCs

Crop and Application Rate	Groundwater EECs: Acute and Chronic (ug/L)	Surface Water EECs (ug/L)*	
		Acute (peak)	Chronic (annual mean)
Corn (Parent only, 1.3 lbs ai/A maximum rate)	0.007	2.2	0.02
Corn (Total toxic residue, 1.3 lb ai/A maximum rate)	4.8	5.4	1.9
Grain Sorghum (Parent only, 2 lbs ai/a maximum rate)	0.01	4.5	0.04
Grain Sorghum (Total toxic residue, 2 lbs ai/a maximum rate)	7.4	13.3	5.5
Sugar Beets (Parent only, 2 lbs ai/A maximum rate)	0.01	1.6	0.009
Sugar Beets (Total toxic residue, 2 lbs ai/A maximum rate)	7.4	4.3	1.3

*In the case of surface water, applications were assumed to be T-banded with 85% of the granules in the top 2 cm of soil.

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Table 5. Summary of Acute and Chronic DWLOC Calculations[a]

Population Subgroup	Acute/Chronic Groundwater (μg/L): Max. EEC[b]	Maximum Surface water EECs (μg/L)[b]		DWLOC (μg/L)	
		Acute	Chronic	Acute	Chronic
U.S. Population	7.4	13.3	5.5	8.1	1.7
Non-nursing infants	7.4	13.3	5.5	0.41	0.45
Children 1-6 yr	7.4	13.3	5.5	1.6	0.48
Children 7-12 yr	7.4	13.3	5.5	2.3	0.49

[a]aPAD = 0.0003 mg/kg/day; cPAD = 0.00005 mg/kg/day
[b]All EECs represent combined residues of terbufos and its sulfoxide and sulfone from the worst-case sorghum scenario.

a. Acute DWLOCs

Maximum acute EECs exceed the acute DWLOCs in all cases, indicating the potential for dietary concern for terbufos residues in drinking water (Table 5). In certain scenarios, eg. the adult/corn combination, the acute DWLOC exceeds the groundwater EEC of 4.8 ppb and the acute surface water EEC of 5.4 ppb. In all cases, acute EECs exceed the applicable acute DWLOC for children. Even if it is assumed that there is no food exposure to terbufos, drinking water sources alone may result in EECs that exceed the DWLOCs, particularly in the case of children. Monitoring data could permit refinement of terbufos exposure through drinking water.

b. Chronic DWLOCs

Chronic EECs exceed the chronic DWLOCs for all population subgroups regardless of the treated crop scenario (Table 5). Therefore, there is potential concern for chronic dietary exposure via drinking water. If it is assumed that there is no food exposure to terbufos, drinking water sources alone may result in EECs that exceed the DWLOCs, particularly in the case of children. Monitoring data could permit refinement of terbufos exposure through drinking water.

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IV. Aggregate Exposure and Risk Assessment

A. Acute Aggregate Exposure and Risk

The Agency is able to quantitate only the food sources of dietary exposure because dietary exposure through drinking water has only been estimated using models. There is no residential exposure to terbufos expected. Acute dietary (food only) risks do not exceed the Agency's level of concern as the most exposed population subgroup, non-nursing infants, has a risk that is 86% of the aPAD (Table 3) based on highly refined exposure estimates. However, based on EECs generated via modeling, the potential exists for residues above the DWLOC from drinking water sources (Tables 4 and 5) even assuming there are no food sources of dietary exposure.

Aggregate short-term and intermediate-term exposures were not estimated because there are no residential exposures expected for terbufos based on the use pattern.

B. Chronic Aggregate Exposure and Risk

In the case of chronic aggregate risk as well, the Agency is able to quantitate only the food sources of dietary exposure as the drinking water residues were estimated from models. In the case of dietary component (food only) of chronic aggregate assessment, risks were below the Agency's level of concern. The most exposed population was, again, non-nursing infants at 9% of the cPAD (Table 3); these risk values were based on highly refined dietary exposure estimates. Again, based upon modeling, the potential exists for dietary exposure via drinking water to exceed the DWLOCs, even if the absence of food sources is assumed.

V. Occupational Exposure and Risk Assessment

A. Incident Data Review

A terbufos human incident review was conducted by J. Blondell (8/23/99, D258891). Data from the national Poison Control Centers (PCCs) over the years 1985-92 reveal 117 cases of occupational exposure to terbufos and 65 cases of nonoccupational exposure. From 1993-96, PCCs reported 27 occupational exposures and 30 nonoccupational exposures; of the occupational cases, none were life-threatening whereas two of the nonoccupational cases were life-threatening. This is viewed as being about a third fewer incidents from 1993-96 than over the 1985-92 period due to increased coverage of the U.S. population by PCCs in recent years. There were no reports of human incidents by the

California Department of Pesticide Regulation/California Pesticide Illness Surveillance Program between 1982 and 1994 although no terbufos usage in California was reported from 1980-1995. Undocumented allegations of terbufos involvement in a poisoning (29 from 1984-91) have been reported by the National Pesticide Telecommunications Network (NPTN). Also undocumented, allegations of terbufos poisoning have been reported by the OPP Incident Data System (IDS); 24 incidents, often serious, were reported with 18 of these occurring outside the U.S., particularly in Central and South America.

B. Occupational Exposure and Risk

Occupational exposure and risk were revised by J. Dawson (8/26/99, D258665). Terbufos is formulated as two granular formulations, a clay-based 15G and a polymer-based 20CR granule. The 15G is marketed only in "Lock-N-Load" closed systems while the 20CR is sold in bags and also in "Lock-N-Load" closed systems. Terbufos is used to control a variety of pests in corn, sugar beets, and sorghum. It is typically applied at-planting with concurrent soil incorporation with ground based application equipment (i.e., row planters) but can also be applied post-emergence or during cultivation activities.

The exposures considered in this risk assessment by the Agency are for the occupational handlers (those involved in the agricultural application) of terbufos. The Agency did not quantitatively consider exposures to terbufos after application because of the manner in which it is applied (i.e., soil incorporation and lack of early season activities minimize the potential for exposure). No terbufos products are intended for sale that homeowners or professional applicators can use in a residential environment. The Agency also believes that the potential for off-target migration of terbufos during agricultural applications is minimal. Therefore, no residential exposure/risk assessment has been completed.

The occupational risk assessment for terbufos has been significantly revised since the preliminary human health risk assessment because the registrant has submitted two formulation-specific dermal toxicity studies and also two chemical- and scenario-specific exposure studies that have been used in the risk assessment (i.e., dermal toxicity studies on the 15G and 20CR formulations and exposure studies on the 15G in "Lock-N-Load" packaging with closed cab application and on the 20CR in bags with open cab application). These exposure data represent the best source of data currently available to the Agency for completing an assessment for terbufos as the data are of high quality and are intended to be specific for the scenarios being considered in this assessment. The chemical- and scenario-specific exposure data (for the 15G and 20 CR formulations) have not been integrated with the Pesticide Handlers

Exposure Database (PHED) for a concurrent analysis because the Agency believes that there are physical differences in the formulations and packaging as well as the levels of personal protection evaluated in the study that preclude combining the data. They are also unique because they represent a slightly higher level of personal protection than is typically considered in the risk assessment process using PHED. Unit exposure values were calculated from each study representing the minimum and maximum monitored values as well as the geometric mean (which is a measure of central tendency of the data). The geometric mean value is the closest approximation of the unit exposure values commonly calculated by the Agency using PHED as the unit exposure reflecting the central tendency of the data.

The registrant used the 15G data (Lock-N-Load/closed cab) to extrapolate to an open loading/open cab application exposure scenario in their submitted risk assessment. The Agency does not believe this is a valid approach given the reliance on unrefined protection factors and that empirical data exist in PHED for this scenario. As a result, the Agency used PHED to consider the open loading and open cab application exposure scenarios for the 15G. The Agency did use the 15G "Lock-N-Load" and closed cab data from the study to consider the 20CR formulation in closed systems and/or closed cab applications.

Using the geometric mean values from the chemical-specific exposure studies as the basis of the assessment, Margins of Exposure (MOEs) are below the Agency's level of concern for the use of terbufos 15G in "Lock-N-Load" packaging and application with closed cabs (with the same levels of personal protective equipment used in the study) if respirators are also used (Table 6). Some scenarios result in exposures above the Agency's level of concern (MOE <100) when the 20CR formulation of terbufos is used in open bags and with open cab application for loaders and combined loader/applicators in the higher usage scenarios (i.e., the lowest MOE for these higher use rate scenarios >60). However, if the 15G study data are used as a surrogate, the Agency has no risk concern for the use of the 20CR in "Lock-N-Load" packaging (about 70% of sales) coupled with closed cab application if a respirator is used because the risks are of no concern for the 15G in the same scenario, the inhalation NOAEL is the same, and the dermal NOAEL (2.0 mg/kg/day) for the 20CR formulation is 6.25 times higher than the NOAEL (0.32 mg/kg/day) for the 15G formulation. Likewise, the Agency has no risk concern when the use of the 20CR in "Lock-N-Load" packaging is coupled with open cab application (based on combination of 15G and 20CR study data) if a respirator is used.

Table 6. Combined Dermal and Inhalation Occupational Margins of Exposure

SCEN.	SCENARIO DESCRIPTOR	CROP TYPE OR TARGET	EXPOSURE FACTORS		15G Lock-N-Load/Closed Cab		20CR Open Bags/Open Cab	
			RATE	ACRES	No Respirator	With Respirator	No Respirator	With Respirator
1b	Loading (apron used instead of coveralls)	Corn	1.1	69	383.9	2386.2	47.4	469.5
			1.3	180	124.5	774.0	15.4	152.3
			1.3	213	105.2	654.1	13.0	128.7
			2.6	69	162.4	1009.5	20.0	198.7
		Sugar Beets	2.6	213	52.6	327.0	6.5	64.4
			1.3	69	324.8	2019.1	40.1	397.3
			1.96	130	114.4	710.8	14.1	139.9
		Sorghum	1.96	213	69.8	433.8	8.6	85.4
			1.3	69	324.8	2019.1	40.1	397.3
			1.96	130	114.4	710.8	14.1	139.9
2b	Application	Corn	1.96	213	69.8	433.8	8.6	85.4
			1.1	69	1147.1	5149.0	2506.5	20984.4
			1.3	180	372.1	1670.1	813.0	6806.5
			1.3	213	314.4	1411.4	687.0	5752.0
			2.6	69	485.3	2178.4	1060.4	8878.0
		Sugar Beets	2.6	213	157.2	705.7	343.5	2876.0
			1.3	69	970.7	4356.8	2120.9	17756.1
			1.96	130	341.7	1533.8	746.6	6250.9
		Sorghum	1.96	213	208.6	936.1	455.7	3815.1
			1.3	69	970.7	4356.8	2120.9	17756.1
			1.96	130	341.7	1533.8	746.6	6250.9
1b & 2b	Loading & Application	Corn	1.96	213	208.6	936.1	455.7	3815.1
			1.1	69	287.6	1630.6	46.5	459.3
			1.3	180	93.3	528.9	15.1	149.0
			1.3	213	78.8	446.9	12.7	125.9
			2.6	69	121.7	689.8	19.7	194.3
		Sugar Beets	2.6	213	39.4	223.5	6.4	62.9
			1.3	69	243.4	1379.7	39.3	388.6
			1.96	130	85.7	485.7	13.8	136.8
		Sorghum	1.96	213	52.3	296.4	8.5	83.5
			1.3	69	243.4	1379.7	39.3	388.6
			1.96	130	85.7	485.7	13.8	136.8
					52.3	296.4	8.5	83.5

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In all cases, where the Agency has risk concerns, **the predominant contributor (i.e., driver) to the overall or total occupational risk is the inhalation component.** This conclusion is supported by the fact that dermal MOEs far exceed 100 based on either the geometric mean or maximum dermal exposure values from the chemical- and scenario-specific data (refer to memo of J. Dawson, 8/26/99, D258665). The large percentage of samples in this study that did not contain detectable terbufos residues should also be considered keeping in mind that the exposure studies are examples of the current state-of-the art and that the analytical aspects of the study are high quality (i.e., the LOD & LOQ values for each sample medium are very low yet yield consistent results).

To summarize, the chemical- and scenario-specific exposure and toxicity data indicate that terbufos formulated as a 15G clay-based granule used with "Lock-N-Load" closed loading systems and concurrent closed cab application presents no risk concern (MOEs >100; Table 6). This is also based on the premise that users wear/use the same levels of personal protective equipment used in the study and a respirator. Terbufos formulated as a 20CR polymeric granule used with "Lock-N-Load" closed systems and either open cab applications or concurrent closed cab applications presents no risk concerns. These scenarios are different than the scenarios monitored in the 20CR exposure study. The Agency does have risk concerns when open bag loading of the 20CR occurs. Inhalation risks are the predominant contributor to the overall risks in this case.

VI. Endocrine Disruptor Effects

EPA is required to develop a screening program to determine whether certain substances (including all pesticides and inerts) "may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or such other endocrine effect..." The Agency is currently working with interested stakeholders, including other government agencies, public interest groups, industry and research scientists in developing a screening and testing program and a priority setting scheme to implement this program. Congress has allowed 3 years from the passage of FQPA (August 3, 1999) to implement this program. At that time, EPA may require further testing of terbufos for endocrine effects.

VII. Cumulative Exposure and Risk

EPA has determined that terbufos has a common mechanism of toxicity with other members of the organophosphates. However, the Agency is in the process of developing methodology to conduct a cumulative risk assessment. For this risk assessment, therefore, EPA will not conduct a cumulative risk assessment.

VIII. Data Needs

The following confirmatory data requirement has been identified:

❑ Toxicology

870.6100 Neurotoxic esterase (NTE) data on the hen are required to support the hen delayed neurotoxicity study.