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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

Office of Prevention, Pesticides
and
Toxic Substances

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DATE: August 30, 1999

MEMORANDUM

SUBJECT: ***TERBUFOS: Comprehensive Report of the Toxicology Endpoints Selection*** **- Report of the Hazard Identification Assessment Review Committee (HIARC)**

FROM: Linda L. Taylor, Ph.D. 8/21/99
Reregistration Branch I
Health Effects Division (7509C)

THROUGH: Jess Rowland , Co-Chair 8/20/99
and
Pauline Wagner, Co-Chair for PW 8/20/99
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: William Hazel, Risk Assessor
Reregistration Branch I
Health Effects Division (7509C)

PC Code: 105001

On July 20, 1999, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) met to re-evaluate the available data on Terbufos to determine whether the selected toxicity endpoints and doses for risk assessment should be revised, based on the new subchronic neurotoxicity study in rats (MRID 44842302). The HIARC concluded that no changes in the selected toxicity endpoints and doses for risk assessment were warranted. Additionally, since the data base on Terbufos is complete, with the exception of confirmatory NTE data, the HIARC concluded that a developmental neurotoxicity study was not required for Terbufos. The HIARC met again on August 12, 1999 to select a dose and endpoint for the AC92100 15G [16.06% a.i.] formulation since this was not done previously. **THIS DOCUMENT SUPERSEDES THE PREVIOUS HIARC DOCUMENTS.**

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Committee Members in Attendance

Members present: William Burnam, Karen Hamernik, Pam Hurley, Susan Makris, Nicole Paquette, Kathleen Raffaele, David Anderson, Virginia Dobozy, Pauline Wagner, Jess Rowland, PV Shah, and Brenda Tarplee (Executive Secretary).

Data was presented by Linda Taylor of Reregistration Branch 1.

Data Presentation and Report Preparation: Linda L. Taylor, Ph.D.
Toxicologist

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I. BACKGROUND

On **January 19, 1995** the Health Effects Division's Toxicology Endpoint Selection Committee (TES) evaluated the toxicology database for Terbufos and selected doses and endpoints for acute dietary and short- and intermediate-term dermal and inhalation occupational/residential exposure risk assessments.

On **September 8, 1997**, the Health Effects Division's Hazard Identification Assessment Review Committee [HIARC] met to evaluate the toxicology data base of Terbufos with special reference to the reproductive, developmental and neurotoxicity data. These data were re-reviewed specifically to address the sensitivity of infants and children from exposure to Terbufos as required by the Food Quality Protection Act (FQPA) of 1996. (HIARC Report dated September 25, 1997). The FQPA requirement was not addressed in the Reregistration Eligibility Document. The HIARC concluded that the Uncertainty Factor for acute and chronic dietary risk assessments was 300, due to the lack of acute and subchronic neurotoxicity studies on Terbufos.

During **May 12 through 14, 1998**, the HIARC conducted a comprehensive review of 40 organophosphates, including Terbufos, for consistency in the doses and endpoints selected for dietary and non-dietary exposures. The HIARC selected the dose and endpoint for the long-term dermal exposure risk assessment not selected previously by the Toxicology Endpoint Selection Committee. Additionally, the HIARC recommended that the 10X FQPA safety factor should be reduced to 3X due to data gaps for the acute and subchronic neurotoxicity studies and NTE data for the hen study **[Hazard Assessment of the Organophosphates: Report of the Hazard Assessment Review Committee dated July 7, 1998]**.

On **June 15 and 16, 1998**, the FQPA Safety Factor Committee (FQPA SFC) evaluated hazard and exposure data for Terbufos and determined that the 10 X to account for enhanced sensitivity of infants and children (as required by FQPA) should be reduced to 3 X because of data gaps for acute and subchronic neurotoxicity studies and NTE data for the hen study **[FQPA Safety Factor Committee of the Organophosphates: A Combined Report of the Hazard Identification Assessment Review Committee and the FQPA Safety Factor Committee dated August 6, 1998]**.

On **November 19, 1998** the HIARC met to evaluate the impact that the results of a recently submitted acute neurotoxicity study in the rat (MRID No. 44672003) would have on risk assessment endpoints. The HIARC determined that the then current acute reference dose, based on the 28-day dog study, would be maintained, due to the apparent sensitivity of the dogs to acute effects **[HED Document Nos. 012993 and 013062, dated 11/23/98 and 1/12/99]**.

On **December 8, 1998**, the HIARC evaluated two 28-day dermal toxicity studies and determined that the toxicity end points and the dose for use in the short- and intermediate-term dermal risk assessments would remain as before, based on cholinesterase activity inhibition in the 28-day dog oral study **[HED Document No. 013031, dated 12/8/98]**.

On **February 3, 1999**, the HIARC reevaluated the reference dose for acute dietary risk assessment, as well as the dermal toxicity endpoint selection for Terbufos. The HIARC evaluated the recently submitted acute neurotoxicity study and determined that the acute neurotoxicity study in rats was more appropriate for the acute dietary assessment since the endpoint (cholinesterase inhibition) was seen following a single oral (gavage) dose and thus suitable for this (acute) risk assessment, rather than the previous endpoint (cholinesterase inhibition) measured at the 7-day time point in the 28-day dietary study in dogs (study

previously used in this risk assessment). Additionally, using a derived species sensitivity factor of 5, the HIARC concluded that the acute neurotoxicity study with an additional 5-fold safety factor would be sufficiently protective. With respect to short- and intermediate-term dermal risk assessment, the HIARC re-reviewed the recently-submitted 28-day dermal toxicity study on the 20 CR end-use product and evaluated its appropriateness for use in short- and intermediate-term exposure risk assessments. Previously, the HIARC selected the 28-day oral dog study for use in these dermal risk assessments. The HIARC determined that the 28-day dermal toxicity study on the 20 CR formulation was appropriate for use in the hazard component of the worker dermal risk assessment for the short-term and intermediate-term time points for the **20 CR formulation [HED Document No. 013238, dated 2/17/99].**

On **July 20, 1999**, the HIARC met to re-evaluate the available data on Terbufos to determine whether the selected toxicity endpoints and doses for risk assessment should be revised, based on the new subchronic neurotoxicity study in rats (MRID 44842302). The HIARC concluded that no change in the selected toxicity endpoints and doses for risk assessment were warranted. With the submission of the subchronic neurotoxicity study, there are no data gaps for the standard Subdivision F Guidelines for Terbufos, with the exception of confirmatory NTE data. The HIARC concluded that a developmental neurotoxicity study was not required for Terbufos since there is no indication of increased susceptibility of rat or rabbit fetuses to *in utero* exposure to Terbufos and no indication of increased susceptibility in the offspring as compared to parental rats following pre-/postnatal exposure, and no neuropathology was observed in any of the studies on Terbufos. Therefore, the HIARC recommended that the FQPA safety factor be removed (1X).

On **August 12, 1999**, the HIARC evaluated the dermal toxicity studies with the formulations again to select a dose and endpoint for dermal risk assessment for the 15 G formulation product. The HIARC, as it had done on February 3, 1999 in the case of the 20 CR formulation, determined that the 28-day dermal toxicity study on the 15 G formulation was appropriate for use as the source of the dose and endpoint to be used in the short-term and intermediate-term dermal occupational risk assessments for the **15 G formulation.**

This report captures all of the essential conclusions reached at these meetings and supersedes the previous TES and HIARC reports.

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II. HAZARD IDENTIFICATION

A. **Acute Dietary (one day)** [Acute RfD] (from HIARC document dated 2/17/99)

Study Selected: Acute Neurotoxicity Study in Rats **Guideline #**: 870.6200; §81-8

MRID No.: 44672003

EXECUTIVE SUMMARY: In an acute oral neurotoxicity study (MRID No. 44672003) 5 groups of 7 week old Sprague-Dawley CD® rats (20/sex/group) were given a single oral dose (by gavage) of Terbufos, 89.7% a.i., in corn oil at doses of 0, 0.15, 0.30, and 0.90 mg/kg of body weight. Before the initiation of the main study, an additional 10 females were exposed to 0.90 mg/kg of Terbufos to determine survivability (satellite study).

Clinical signs such as ano-genital stains, oral stains, lethargy, reduced defecation and food consumption were observed in females treated with 0.90 mg/kg of the test substance (main study and satellite study). A red exudate from the eye was reported in one male treated at the 0.30 mg/kg dose level. These symptoms did not persist beyond day 5 of the study. One female treated at the 0.90 mg/kg dose level died 5.5 hours after treatment with the test article. No other mortalities were reported during the test period.

The first indication of a compound-related effect (miosis) detected by the FOB was reported at the 0.3 mg/kg and 0.90 mg/kg doses approximately 6 hours after exposure to the test substance in both males and females. In addition to miosis, females at the 0.90 mg/kg dose level showed evidence of excessive salivation, lacrimation, ataxia, stupor, soiled coat, decreased forelimb strength, slightly impaired locomotion, and tremors. These symptoms resolved within the first week after treatment with the test article and were no longer evident at the Day 7 observation period.

Ten animals/sex/dose were tested for plasma, erythrocyte, and brain cholinesterase activity (PChE, RChE, and BChE, respectively). Significant cholinesterase inhibition was reported in both males and females at the 0.30 mg/kg and 0.90 mg/kg doses.

Gross necropsy examination and histopathology testing of animals that were euthanized at the end of the study revealed no compound-related abnormalities.

The NOAEL for acute neurotoxicity and plasma cholinesterase inhibition is 0.15 mg/kg/day, and the LOAEL is 0.30 mg/kg, based on the findings of the FOB testing and cholinesterase inhibition.

Dose and Endpoint for Establishing the Acute RfD: NOAEL of 0.15 mg/kg, based on miosis in males and plasma cholinesterase inhibition at the LOAEL of 0.30 mg/kg in males and females.

Comments about Study/Endpoint: *This dose and endpoint replace the previous [TES and 9/8/97 HIARC] oral NOAEL based on the 28-day dog study and the 7-day measurement of cholinesterase activity inhibition.* The effects observed in the acute neurotoxicity study occurred after a single exposure, which is appropriate for the acute risk assessment, and the principal toxicological endpoint of concern [cholinesterase inhibition] was observed in this study.

Uncertainty Factor: 500 (10x for interspecies extrapolation and 10x for intraspecies variability and 5x

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for differences in sensitivity between dog and rat. The additional uncertainty factor (5x) is required based on the analysis of plasma cholinesterase inhibition time course in the 90-day oral rat and 28-day oral dog study. The analysis was performed in an attempt to determine a species sensitivity factor that could be applied to the oral acute neurotoxicity study in the rat so that the rat study could be used for the acute dietary endpoint. The HIARC had previously selected a 28-day oral dog study which had a plasma cholinesterase measurement at day 7 for the acute dietary endpoint. Using the rat acute neurotoxicity study for the endpoint with a derived species sensitivity factor would have the advantage of the appropriate time-related endpoint, but still take into account the sensitivity differences between the rat and the dog.

The graphical analysis of the data at 1, 2, and 4 weeks revealed an approximate five-fold difference in sensitivity between the two species with the dog being the more sensitive. The graphs plotted dose (mg/kg) versus percent plasma cholinesterase inhibition at each of the time points. The Committee agreed with the analysis and felt that using the acute oral rat neurotoxicity study with an additional 5-fold safety factor would be sufficiently protective.

$$\textbf{Acute RfD} = \frac{\textbf{0.15 mg/kg}}{\textbf{500 (UF)}} = \textbf{0.0003 mg/kg}$$

This Risk Assessment is Required.

B. Chronic Dietary : [Reference Dose (RfD)] (from HIARC document dated 9/25/97)

Study Selected: 1-year/28-day oral study (dog) **Guideline #:** 870.4100/§83-1

MRID No.: 00263678

Executive Summary: In a 1-year oral toxicity study (Accession No. 00263678), male and female Beagle dogs (6 per sex/group) were given Terbufos (89.6%) *via* corn oil capsules at concentrations of 0, 15, 60, 90 [initially 240 until week 8], and 120 [initially 480 until week 7] µg/kg/day. Control dogs [8/sex] received corn oil capsules.

Treatment-related deaths occurred at the initial mid-high [one female] and initial high-dose [one male and three females] levels. Behavioral changes associated with cholinesterase inhibition [tremors, listless ness, excessive salivation, weak hind legs, diarrhea/red-tinged feces] were also observed in both sexes at these two dose levels [one male and three females at the mid-high dose; three males and 6 females at the high dose]. Following the reduction in dose levels, the overt signs of cholinesterase inhibition disappeared. Both sexes at the high-dose level lost weight during the first 7 weeks prior to the reduction in dose level. Males [65% of control] and females [57% of control] at the mid-high dose level displayed lower body-weight gains during the same time interval. Thereafter, both sexes and dose levels displayed a greater body-weight gain than the controls. Plasma cholinesterase activity was consistently depressed at all dose levels in both sexes throughout the study [≈40% at low, >60% all other dose levels]. RBC cholinesterase activity was depressed throughout the study in both sexes at the two highest dose levels only. With respect to brain cholinesterase activity, there was a dose-related decrease in cerebral cholinesterase activity in the males but comparable values were observed in cerebellar cholinesterase activity. In the females, there was no dose response in cerebral activity but cerebellar cholinesterase activity was decreased at the two highest dose levels [dose-related].

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In a 28-day oral study in dogs [MRID 40374701] performed specifically to define the plasma cholinesterase activity NOAEL, plasma cholinesterase inhibition was observed at dose levels of 2.5 µg/kg/day [14%-23%] and above. The TES Committee determined that the NOAEL for plasma cholinesterase activity was 5 µg/kg/day.

The NOAEL for plasma cholinesterase activity is 5 µg/kg/day.

Dose and Endpoint for Establishing the RfD: NOAEL = 0.005 mg/kg/day, based on plasma ChE inhibition in male and female dogs at 0.015 mg/kg/day. This chronic RfD is the same as that established by the RfD/QA Peer Review Committee HED Document No. 011982, dated 7/1/96].

Uncertainty Factor (UF): An uncertainty factor of 100 was applied to account for both interspecies and intraspecies extrapolation.

$$\textbf{Chronic RfD} = \frac{\textbf{0.005 mg/kg}}{\textbf{100 (UF)}} = \textbf{0.00005 mg/kg/day}$$

This Risk Assessment is Required.

C. Occupational/Residential Exposure - Dermal

1. Dermal Absorption (from TES HED Doc #No. 013140 (01/19/95)

Dermal absorption studies are not available. A dermal absorption factor is not required since dermal NOAELs were selected for dermal risk assessments.

% absorbed: Not applicable.

2. Short-Term Dermal Exposure (1-7 days)

Study Selected: 28-Day Dermal Toxicity Study in Rats Guideline 870.3200/§82-2

MRID No.: 44690501

Executive Summary: In a repeated 28-day dermal toxicity study (MRID 44690501), female Sprague Dawley rats (10 rats/dose) were treated dermally [10%-15% of total body surface] with an unpulverized 20 CR formulation of Terbufos (20.65% a.i.) as neat material moistened with saline at doses of 0, 5 and 10 mg/kg/day [1 and 2 mg a.i./kg/day, respectively] for 6 hours/day, 5 days a week for 4 weeks. Sites were covered with a gauze bandage. In the range-finding study [MRID 44450601], Sprague-Dawley rats [3/sex/group] were treated dermally as above with Terbufos CR formulation [20.72% a.i.] at dose levels of 0, 10, 25, 50, and 125 mg/kg/day [2, 5, 10, and 25 mg a.i./kg/day, respectively].

In the **main study**, no mortality was observed and there were no biologically-significant or treatment-related effects on clinical signs, body weight, body-weight gain, or food consumption. There were no effects observed on plasma, RBC, or brain cholinesterase activity at any time point. No dermal irritation was observed. In the **range-finding study**, two of the three females at the highest dose level were found dead [days 12 and 13]. All other rats survived. Males at the highest dose level displayed a decreased

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body-weight gain at day 26 only compared to the controls. Body-weight gains were comparable among the groups at all other dose levels [both sexes]. Signs of cholinergic toxicity [tremors, excessive salivation, irregular gait, labored breathing, anogenital staining] were observed occasionally in both sexes at the highest dose level [day 9 on]. Plasma cholinesterase activity was depressed at the three highest dose levels in both sexes [19%-62%, 40%-74%, and 58%-96% with increasing dose, respectively] at all time points measured. RBC cholinesterase activity was depressed in both sexes at the three highest dose levels throughout the study [34%-73%, 56%-86%, and 81%-98% with increasing dose, respectively], but only on day 26 in females at 10 mg/kg/day. Brain cholinesterase activity was depressed at the highest dose level in both sexes [males 54%/females 78%], and both sexes at the next two dose levels displayed non-significant decreases [12%-25%] in brain cholinesterase activity.

The NOAEL is 10 mg/kg/day [2 mg a.i./kg/day], based on plasma cholinesterase inhibition in both sexes at 25 mg/kg/day [5 mg a.i./kg/day] (LOAEL).

Dose and Endpoint for Risk Assessment: NOAEL = **2 a.i.** mg/kg/day, based on plasma ChE inhibition at 5 a.i. mg/kg/day for the **CR formulation.**

Comments about Study/Endpoint: *This dose and endpoint replace the previous selection [TES document]; both were selected by the HIARC at the 2/3/99 meeting [HED Document No. 013238].* The effects observed in the dermal toxicity study occurred throughout the 28-day exposure period. The route of exposure [dermal] is appropriate for this dermal risk assessment, and the principal toxicological endpoint of concern [cholinesterase inhibition] was observed in this study. **NOTE: If exposure is in terms of the formulated product, use the NOAEL of 10 mg/kg/day. If exposure is in terms of the active ingredient, use the NOAEL of 2 mg/kg/day.**

Study Selected: 28-Day Dermal Toxicity Study in Rats Guideline 870.3200/§82-2

Executive Summary: In a 28-day dermal toxicity study (MRID No. 44520501), AC 92100 15G (terbufos, 16.06% a.i.) was administered topically to the clipped dorsal region (intact skin) of Sprague Dawley [Crl:CD BR] rats (10/sex/dose). Animals received daily dose of 0, 2, 5, 10 or 25 mg AC 92100 15G/kg/day (0, 0.32, 0.8, 1.6 or 4.0 mg a.i./kg/day) for 6 hours per day, 5 days per week, for 4 weeks. Animals were weighed before study initiation, weekly and at study termination. Plasma and erythrocyte cholinesterase determinations were performed on days 1, 5, 12, and 26 (at termination). At necropsy, the right halves of brains were analyzed for cholinesterase activity.

There were no statistically significant treatment-related effects on dermal reactions. No treatment-related effects on body weight, mortality, food consumption, hematology, blood chemistry, organ weights, gross or microscopic pathology were observed. Clinical signs related to cholinesterase inhibition such as localized fine tremors in the forepaws and hindlegs were seen during weeks 3 and 4 in females treated at 25 mg/kg/day.

There was a statistical significant reduction in plasma cholinesterase activity in males treated at 5 mg/kg/day or above (ranged from 17% to 60%) and in both males and females treated at 10 or 25 mg/kg/day (38% to 93%).

There was a statistical significant reduction in erythrocyte cholinesterase activity in both males and females treated at 10 or 25 mg/kg/day (ranged from 31% to 96%).

There was a statistical significant reduction in brain cholinesterase activity in males treated at 5, 10

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or 25 mg/kg/day and in females treated at 10 or 25 mg/kg/day (ranged from 18% to 70%). **No dermal irritation was observed in this study; the NOAEL for dermal irritation is equal to or greater than 25 mg/kg/day (4 mg/kg/day a.i., HDT). The cholinesterase LOAEL is 5 mg/kg/day (0.8 mg/kg/day a.i.) based on statistically significant inhibition of plasma cholinesterase (ranged from 17.2% to 18.6% relative to controls) and brain cholinesterase activity (8.9%). The cholinesterase NOAEL is 2 mg/kg/day (0.32 mg/kg/day a.i.).**

Dose and Endpoint for Risk Assessment: NOAEL = **0.32 a.i.** mg/kg/day, based on plasma and brain ChE inhibition at 0.8 a.i. mg/kg/day for the **AC92100 15 G formulation.**

Comments about Study/Endpoint: *This dose and endpoint replace the previous selection [TES document]; both were selected by the HIARC at the 2/3/99 meeting [HED Document No. 013238].* The effects observed in the dermal toxicity study occurred throughout the 28-day exposure period. The route of exposure [dermal] is appropriate for this dermal risk assessment, and the principal toxicological endpoint of concern [cholinesterase inhibition] was observed in this study. **NOTE: If exposure is in terms of the formulated product, use the NOAEL of 2 mg/kg/day.**

This Risk Assessment is Required

3. Intermediate Term Dermal Exposure

Study Selected: 28-Day Dermal Toxicity Studies in Rats [15G & 20 CR] Guideline 870.3200/§82-2

MRID No.: 44690501 and 44520501

Executive Summaries: see under Short-Term dermal.

Dose and Endpoint for Risk Assessment: NOAEL = 2 a.i. mg/kg/day, based on plasma ChE inhibition at 5 a.i. mg/kg/day for the **CR formulation.**

Comments about Study/Endpoint(s): *These doses and endpoints replace the previous selection [TES document] of dose and endpoint selected by the HIARC at the 2/3/99 meeting [HED Document No. 013238].* The effects observed in the dermal toxicity studies occurred throughout the 28-day exposure period. The route of exposure [dermal] is appropriate for this dermal risk assessment for both formulations, and the principal toxicological endpoint of concern [cholinesterase inhibition] was observed in both studies. **NOTE: If exposure is in terms of the formulated product, use the NOAEL of 10 mg/kg/day.**

Dose and Endpoint for Risk Assessment: NOAEL = 0.32 a.i. mg/kg/day, based on plasma and brain ChE inhibition at 0.8 a.i. mg/kg/day for the **15 G formulation.**

Comments about Study/Endpoint(s): *These doses and endpoints replace the previous selection [TES document] of dose and endpoint selected by the HIARC at the 2/3/99 meeting [HED Document No. 013238].* The effects observed in the dermal toxicity studies occurred throughout the 28-day exposure period. The route of exposure [dermal] is appropriate for this dermal risk assessment for both formulations, and the principal toxicological endpoint of concern [cholinesterase inhibition] was observed in both studies. **NOTE: If exposure is in terms of the formulated product, use the NOAEL of 2 mg/kg/day.**

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This Risk Assessment is Required.

4. Long Term Dermal Exposure

The use pattern [1-2 applications/year at 1.3 to 4 pounds a.i. per acre] does not indicate a potential for long-term dermal exposure. Therefore, this risk assessment is not required.

5. Inhalation [any time period]

Study Selected : subchronic inhalation study - rats **Guideline #:** OPPTS 870.3465/§82-4

MRID No.: 00258710

Executive Summary: Groups of 10 Sprague-Dawley rats/sex/group were exposed to vapors of technical Counter Terbufos for 3 weeks [8 hours/day, 5 days/week] at target concentrations of 0, 0.005, 0.01, 0.05, and 0.10 mg/m^3 and observed for an additional 2 weeks [Accession No. 258710]. During the first week of exposure, the mean analytical concentrations ranged from 2 to 44 percent of target concentrations. Because of these low values, the rats were exposed for an additional 2 weeks for a total of 3 weeks. The mean analytical concentrations of test material for weeks 2 and 3 were 0.0117, 0.0243, 0.0458, and 0.0946 mg/m^3 for males and 0.0112, 0.0256, 0.0468, and 0.1001 mg/m^3 for females. Chamber concentrations were not well controlled, and wide variations in the daily concentration were noted. Two females that were exposed to 0.1001 mg/m^3 died during week 3 following signs of cholinesterase inhibition. At the conclusion of the exposure phase, brain cholinesterase was significantly lower for males and females exposed to a target concentration of 0.1 mg/m^3. Histopathological evaluations were not performed. Although the mean concentrations for the males in the two highest dose groups were 0.0458 mg/m^3 and 0.094 mg/m^3, respectively, the lowest daily mean chamber concentrations were selected as the values for the NOAEL and LOAEL. **The NOAEL is 0.0098 mg/m^3 and the LOAEL is 0.0394 mg/m^3, based on brain cholinesterase inhibition.**

Dose and Endpoint for Risk Assessment: NOAEL = 0.01 µg/l, based on RBC, plasma, and brain cholinesterase inhibition at LOAEL of 0.04 µg/L.

Comments on Study/Endpoint: This NOAEL should be used for short-term and intermediate-term exposure risk assessments. Based on the use pattern [see Long-Term Dermal], there is no potential long-term inhalation exposure risk. Therefore, long-term inhalation risk assessment is not required. The route of exposure [inhalation] is appropriate for this inhalation risk assessment, and the principal toxicological endpoint of concern [cholinesterase inhibition] was observed in this study. *The study, dose, and endpoint are the same as those established by the TES Committee in 1995.*

This Risk Assessment is Required.

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D. Margins of Exposure

A margin of exposure (MOE) of 100 is consdered to be adequate for occupational exposure risk assessments (there are currently no registered residential uses) since there is no evidence that the species sensitivity observed via the oral route of administration would also occur via the dermal route. Additionally, it has been shown that rat skin is more permeable than human skin and since a dermal NOAEL from a 28-day dermal study in rats is used for dermal exposure risk assessments, the MOE of 100 is considered to be adequate.

E. Recommendation for Aggregate Exposure Risk Assessment

Since there are no residential uses, aggregate exposure risk assessment will be limited to food and water. For acute exposure, add the food and water using the high end exposure combined with the acute RfD.

III. CLASSIFICATION OF CARCINOGENIC POTENTIAL

Terbufos has been classified as a Group E chemical based on the lack of evidence of carcinogenicity.

IV. FQPA CONSIDERATIONS

1. Neurotoxicity

In an acute delayed neurotoxicity study, no delayed neurotoxicity was seen in hens given a single oral dose of Terbufos at 40 mg/kg (MRID No. 00037472). The HIARC Committee noted that this study did not assess for the potential of Terbufos to inhibit neurotoxic esterase (NTE) in hens.

In an acute oral neurotoxicity study (MRID No. 44672003) 5 groups of 7 week old Sprague-Dawley CD® rats (20/sex/group) were given a single oral dose (by gavage) of Terbufos, 89.7% a.i., in corn oil at doses of 0, 0.15, 0.30, and 0.90 mg/kg of body weight. Before the initiation of the main study, an additional 10 females were exposed to 0.90 mg/kg of Terbufos to determine survivability (satellite study).

Clinical signs such as anogenital stains, oral stains, lethargy, reduced defecation and food consumption were observed in females treated with 0.90 mg/kg of the test substance (main study and satellite study). A red exudate from the eye was reported in one male treated at the 0.30 mg/kg dose level. These symptoms did not persist beyond day 5 of the study. One female treated at the 0.90 mg/kg dose level died 5.5 hours after treatment with the test article. No other mortalities were reported during the test period.

The first indication of a compound-related effect (miosis) detected by the FOB was reported at the 0.3 mg/kg and 0.90 mg/kg doses approximately 6 hours after exposure to the test substance in both males and females. In addition to miosis, females at the 0.90 mg/kg dose level showed evidence of excessive salivation, lacrimation, ataxia, stupor, soiled coat, decreased forelimb strength, slightly impaired locomotion, and tremors. These symptoms resolved within the first week after treatment with the test article and were no longer evident at the Day 7 observation period.

Ten animals/sex/dose were tested for plasma, erythrocyte, and brain cholinesterase activity (PChE, RChE, and BChE, respectively). Significant cholinesterase inhibition was reported in both males and females at the 0.30 mg/kg and 0.90 mg/kg doses.

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Gross necropsy examination and histopathology testing of animals that were euthanized at the end of the study revealed no compound-related abnormalities.

Under the conditions of this study, the **NOAEL** for acute neurotoxicity and plasma cholinesterase inhibition is 0.15 mg/kg/day. Given the findings of the FOB testing and cholinesterase inhibition, the **LOAEL** is established at 0.30 mg/kg/day.

This study is **acceptable** and satisfies the guideline requirements for an acute oral neurotoxicity study (OPPTS 870.6200/§81-8) in the rat.

In a subchronic neurotoxicity study (MRID 44842302), Terbufos [AC 92100] (89.7% a.i.) was administered in the diet to 20 Crl:CD (SD) IGS BR rats/sex/dose at dose levels of **0 ppm, 0.5 ppm, 0.8 ppm, or 5.0 ppm [males]/3.0 ppm [females]** for at least 85 days [10 rats/sex/cholinesterase group] or 13 weeks [10 rats/sex/neurobehavioral group]. These dose levels corresponded to **0.036, 0.059, and 0.369 mg/kg/day, respectively, in males; 0.042, 0.064, and 0.251 mg/kg/day, respectively, in females.**

No adverse or treatment-related effects were observed on mortality or clinical signs. The high-dose males displayed slightly decreased body weights [94%-97% of control] throughout the study compared to the controls, but the high-dose females displayed body weights that were comparable to or greater than the controls throughout the study. Body-weight gains were decreased [86%-93% of control] in the high-dose males throughout the study, although the magnitude of the deficit diminished with time. There was no adverse effect on body-weight gain in the females. Food consumption was comparable to/greater than the control in the treated groups [both sexes].

There were no treatment-related effects observed on ophthalmoscopy, and motor activity was comparable among the groups for both sexes throughout the study. There were no significant and treatment-related differences relative to the controls in any of the parameters monitored in the functional observational battery in either sex.

There was a dose-related inhibition of plasma cholinesterase activity [males ≈70%/females ≈90% inhibition] and RBC acetylcholinesterase activity [≈100% inhibition] throughout the study in both sexes. At study termination, brain cholinesterase activity [males 55%-58%/females 68%-71% inhibition] was decreased at the high-dose level in both sexes, with the magnitude of the inhibition greater in the females than in the males.

No treatment-related macroscopic and microscopic lesions were observed in either sex. Brain weight data were not provided.

The NOAEL for systemic toxicity is 0.8 ppm [0.059 mg/kg/day], and the LOAEL for systemic toxicity is 5 ppm [0.369 mg/kg/day], based on decreased body weight and body-weight gains in males. No neurobehavioral or neuropathological effects were observed in either sex.

The NOAEL for inhibition of plasma cholinesterase and RBC acetylcholinesterase activity [both sexes] is 0.5 ppm [0.036 (males)/0.042 (females) mg/kg/day] and the LOAEL for inhibition of plasma cholinesterase and RBC acetylcholinesterase activity [both sexes] is 0.8 ppm [0.059

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(males)/0.064 (females) mg/kg/day].

The NOAEL for brain cholinesterase activity is 0.8 ppm [0.059 (males)/0.064 (females) mg/kg/day] and the LOAEL for brain cholinesterase activity is 5 (males)/3 (females) ppm [0.369 (males)/0.251 (females) mg/kg/day].

This guideline subchronic neurotoxicity study is **Acceptable [OPPTS 870.6200; §82-7],** and it satisfies the guideline requirement for a subchronic neurotoxicity study in rats.

Neurotoxicity has been observed in other studies on Terbufos, as evidenced by tremors, listlessness, and weak hind legs in both sexes in the chronic oral toxicity study in dogs; tremors in the acute dermal/inhalation toxicity studies and subchronic inhalation study; tremors, irregular gait in 4-week dermal toxicity studies.

2. Developmental Toxicity

A. Prenatal Developmental Toxicity Study in Rats

The NOAEL, LOAEL and endpoint selected for maternal and developmental toxicity in the prenatal developmental toxicity study in rats are shown in Table 1.

Table 1. NOAELs/LOAELs & ENDPOINTS FOR DEVELOPMENTAL TOXICITY STUDIES IN RATS

CHEMICAL	MATERNAL TOXICITY			DEVELOPMENTAL TOXICITY		
	(mg/kg/day)		ENDPOINT	(mg/kg/day)		ENDPOINT
	NOAEL	LOAEL		NOAEL	LOAEL	
TERBUFOS	≥0.2	NA	no maternal toxicity at HDT	0.1	0.2	Increases in early fetal resorptions, # of litters with 2 or more resorptions, & postimplantation losses

Subsequent to the original assessment by the HIARC, a further analysis of this study was conducted (*Memorandum:* B. Tarplee to W. Hazel dated August 2, 1999; HED Doc. No.013598). It was determined that the HIARC report of the May 12, 13, and 14, 1998 meeting was erroneous in that the maternal and developmental LOAELs and NOAELs were not at the same dose level in the developmental toxicity study in rats. However, there is not a concern for the apparent quantitative increased susceptibility since oral studies with Terbufos demonstrate that had cholinesterase been measured, inhibition would most likely have been observed in the dams at the developmental LOAEL (0.2 mg/kg/day). Cholinesterase inhibition occurred after a single oral dose of 0.3 mg/kg in the acute neurotoxicity study in rats (MRID No: 44672003) but not at 0.15 mg/kg; and after repeated oral dosing at 0.25 mg/kg/day in the subchronic neurotoxicity study in the female rats (MRID No. 44842302).

The developmental LOAEL was conservatively established for fetal effects seen at the 0.2 mg/kg/day dose level. The results of the range-finding study indicate that this is approaching a dose that would cause severe maternal toxicity: death occurred in the dams in the range-finding study at 0.4

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mg/kg/day.

Although the HIARC did not dispute the dose level at which the developmental LOAEL was established, it is noted that the increase in resorptions observed in the rat developmental study was minimal [resorptions/dam 0.83, 0.5, 1.2, 1.3 with increasing dose] with no statistical significance when compared to concurrent controls. Additionally, the increase in resorptions at 0.2 mg/kg/day in the rat developmental study was contrary to the results in the range-finding study wherein a decrease in resorptions was observed at the 0.2 mg/kg/day dose level [control 1 *vs 0.6 at 0.2 mg/kg/day and 1.7 at 0.05 mg/kg/day]*. Also at the high dose, the incidence of post-implantation loss was only minimally outside of the reported historical control range for the performing laboratory (1.3 vs. 1.2). The number of live fetuses per dam at cesarean section for the 0.2 mg/kg/day dose group was also found not to be significantly decreased [15 in control *vs*. 13.7 at mid- and 13.6 at high-dose levels]. Also in the range-finding study, the number of live fetuses at 0.2 mg/kg/day [15.0] was comparable to the control [15.8].

In summary, a weight-of-evidence analysis of the toxicity data base for terbufos indicates there is no concern for quantitative or qualitative increased susceptibility to rats following pre- /or postnatal exposure in the developmental and reproductive toxicity studies.

B. Prenatal Developmental Toxicity Study in Rabbits

For Terbufos, the NOAEL and LOAEL were lower for maternal toxicity than for developmental toxicity [i.e., effects noted in offspring occurred at maternally toxic doses or higher; Table 2].

Table 2. NOAELs/LOAELs & ENDPOINTS FOR DEVELOPMENTAL TOXICITY STUDIES IN RABBITS

CHEMICAL	MATERNAL TOXICITY			DEVELOPMENTAL TOXICITY		
	(mg/kg/day)		ENDPOINT	(mg/kg/day)		ENDPOINT
	NOAEL	LOAEL		NOAEL	LOAEL	
TERBUFOS	0.1	0.25	Clinical signs [soft stool] and decreased body weight gain.	0.25	0.5	Increased resorptions % decreased fetal body weight.

3. Reproductive Toxicity

Two-Generation Reproduction Study in Rats

The NOAEL, LOAEL, and endpoints selected for the parental systemic and offspring toxicity in the two-generation reproduction study is shown in Table 4.

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Table 4. NOAELs/LOAELs & ENDPOINTS FOR THE 2-GENERATION REPRODUCTION TOXICITY STUDIES IN RATS						
CHEMICAL	PARENTAL SYSTEMIC TOXICITY			OFF SPRING TOXICITY (mg/kg/day)		
	(mg/kg/day)		ENDPOINT	(mg/kg/day)		ENDPOINT
	NOAEL	LOAEL		NOAEL	LOAEL	
TERBUFOS	1 ppm [0.08]	0.22	Decreased body weight gain during lactation.	1 ppm [0.07]	0.17	Decreased in pregnancy rate & male fertility.

4. Determination of Susceptibility

There is **no evidence of increased sensitivity,** based on an adequate 2-generation reproduction study in rats, an adequate rat developmental toxicity study, and an adequate rabbit developmental toxicity study.

No evidence of enhanced susceptibility was observed for Terbufos following *in utero* exposure to pregnant rats. The biological significance of the fetal effects (increases in early fetal resorptions and postimplantation losses) are questionable since similar effects (i.e., decreased litter size) were not seen in the two-generation reproduction study in rats. Additionally, based on the results of other studies with this chemical, substantial cholinesterase inhibition may have occurred in the dams (not measured in the developmental study) and thus most likely contributed to the fetal effects.

No evidence of enhanced susceptibility was observed for Terbufos following *in utero* exposure to pregnant rabbits. The developmental toxicity NOAEL was observed at a level that produced maternal toxicity.

No evidence of enhanced susceptibility was observed for Terbufos following pre and/or postnatal exposure in the two-generation reproduction study in rats [i.e., effects noted in offspring occurred at maternally toxic doses or higher]. Plasma, RBC, and brain cholinesterase activity were depressed in both generations in both sexes of the adult rats at sacrifice.

5. Cholinesterase Inhibition

Cholinesterase activity was not measured in the adults and offspring in the developmental toxicity studies. In the reproduction study, ChE activity was measured at sacrifice in adult rats only [P1 and F1]. There were dose-related decreases in plasma and red blood cell cholinesterase activities in both sexes at the mid- [females] and high-dose levels in both generations. Brain cholinesterase activity was inhibited in females at the mid-dose level and in both sexes at the high-dose level.

6. Determination of Need For Developmental Neurotoxicity Study

There are sufficient data available to adequately assess the potential for toxicity to young animals following pre-and/or post-natal exposure to Terbufos. These include acceptable developmental toxicity studies in rats and rabbits, as well as a 2-generation reproduction studies in rats. In addition, no treatment-related neuropathology was seen after acute and subchronic exposure to rats. There was no evidence of abnormalities to the fetus to the fetal nervous system in the pre- and post-natal studies. **Based on the weight-of-evidence, the HIARC determined that a developmental neurotoxicity study in rats is not required for Terbufos.**

7. **HIARC Recommendation of the FQPA Safety Factor**

Previously for Terbufos, the FQPA safety factor recommendation was 3X due to the data gaps for the acute and subchronic neurotoxicity studies (*FQPA Safety Factor Recommendations for the Organophosphates* dated August 6, 1998). These data requirements have been satisfied, and **the HIARC Committee recommended that the FQPA safety factor be removed (1X).**

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Acute Toxicity Endpoints

The table below 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	-
870.2500/§81-5	Primary Skin Irritation	all rabbits died	-
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

IV. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

Toxicological endpoints for risk assessments with Terbufos are tabulated below:

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	NOAEL= 0.15 UF = 500	Miosis in males; 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 a.i.	plasma, RBC, brain ChE Inhibition observed at higher doses in range-finding study	28-Day Dermal Study on 20 CR formulation in Female Rats
Short- and Intermediate-Term (Dermal) *15G only*	NOAEL = 0.32 a.i.	Plasma and brain ChE Inhibition	28-Day Dermal Study on 15G formulation in Rats
Long-Term Dermal	The use pattern [1-2 applications/year at 1.3 to 4 pounds a.i. per acre] does not indicate a potential for long-term dermal exposure. This risk assessment is not required.		
Short- and Intermediate-Term [Inhalation]	NOAEL= 0.00001 mg/L	Plasma , RBC, brain ChE Inhibition	Subchronic Inhalation Study in Rats
Long-Term Inhalation	The use pattern [1-2 applications/year at 1.3 to 4 pounds a.i. per acre] does not indicate a potential for long-term inhalation exposure. This risk assessment is not required.		

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

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Hazard Characterization

Terbufos [S-[[(1,1-dimethylethyl)thio]methyl]O,O-diethyl phosphorodithioate; S-(tert-butylthio)methyl O,O-diethyl-phosphorodithioate; S-tert-butylmercaptomethyl O,O-diethyl dithiophosphate] is an organophosphate insecticide/nematicide registered for use on corn, grain sorghum, and sugar beets.

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, and decreased cholinesterase activity [RBC, plasma, brain] 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].

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 litter 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. The proposed final step is S-oxidation.

IV. DATA GAPS

None. The toxicology database for Terbufos is complete. Confirmatory NTE data are required for the hen study.

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