DATE: **December 3, 1997**

MEMORANDUM

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SUBJECT: **TRIBUFOS - *FQPA REQUIREMENT*** - Report of the Hazard Identification Assessment Review Committee.

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BACKGROUND: On November 25, 1997, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) met to re-evaluate the Uncertainty Factors and MOEs for dietary as well as non-dietary risk assessments in the RfD and TES Committee meetings. This re-evaluation was necessitated to ensure consistency with the other organophosphate chemicals that were recently reviewed by the HIARC to address the enhanced sensitivity of infants and children as required by the FQPA. HIARC's conclusions are attached.

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A. INTRODUCTION

On January 23, 1997, the Health Effect's Division's RfD/Peer Review Committee evaluated the toxicology data base of Tribufos and reassessed the Reference Dose and concluded that the use of an additional Uncertainty Factor for enhanced sensitivity for infants and children (as required by FQPA) was not warranted. This decision was based on the lack of evidence of increased sensitivity in the developmental studies in rats and rabbits and the two-generation reproduction study in rats (Memo: G. Ghali, HED to P. Errico, RD, dated 07/14/97).

On January 28, 1997 the Health Effects Division's Toxicology Endpoint Selection (TES) Committee selected the doses and endpoints for acute dietary as well as occupational and residential exposure risk assessments but did not address the Margins of Exposure (MOEs) required for the various exposure scenarios.

On November 25, 1997, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) met to re-evaluate the Uncertainty Factors and MOEs for dietary as well as non-dietary risk assessments in the RfD and TES Committee meetings. This re-evaluation was necessitated to ensure consistency with the other organophosphate chemicals that were recently reviewed by the HIARC to address the enhanced sensitivity of infants and children as required by the FQPA. HIARC's decisions are summarized below.

The reader is referred to the initial RfD and TES Committee reports for summaries of the studies as well as the rationale for the doses and endpoints selected for the various exposure scenarios. The decisions made by HIARC on the Uncertainty Factors and/or the Margins of Exposure for acute and chronic dietary as well as occupational/residential risk assessments are provided below.

B. DETERMINATION OF UNCERTAINTY FACTORS AND/OR MARGINS OF EXPOSURES

1. Neurotoxicity

- Acute and subchronic neurotoxicity studies in rats are not available and thus data on cholinesterase inhibition and FOB as well as histopathology of the central and peripheral nervous systems are not available for evaluation after single or repeated exposures to Tribufos.

- In a subchronic dermal delayed neurotoxicity study in hens, Tribufos was applied to the comb of the hen at doses of 0, 2.6, 11 or 42 mg/kg/day for 90-days. Triorthocresophosphate (TOCP) was the positive control. Treatment-related effects observed included decrease in body weight gain in hens at 11 mg/kg/day, ataxia in 7 of 11 hens at 42 mg/kg/day and whole blood cholinesterase inhibition in hens at 2.6 mg/kg/day. Histopathology indicative of neurotoxicity was observed primarily in the brain and spinal cord of hens at 42 mg/kg/day. A NOEL was not established and the LOEL was 2.6 mg/kg/day based on the whole blood cholinesterase inhibition.

2. Developmental Toxicity

- The developmental toxicity studies in rats and rabbits showed no evidence of additional sensitivity of young rats or rabbits following pre- or postnatal exposure to Tribufos.

- In a prenatal developmental toxicity study, pregnant Sprague-Dawley rats received oral administration of Tribufos at doses of 0, 7, or 28 mg/kg/day during gestation days 6 through 15. For maternal toxicity, the NOEL was 1 mg/kg/day and the LOEL was 7 mg/kg/day based on inhibition of plasma and red blood cell cholinesterase activity. No developmental toxicity was observed. For developmental toxicity, the NOEL was ≥28 mg/kg/day (HDT); a LOEL was not established (MRID No. 40190601).

- In a prenatal developmental toxicity study, pregnant American Dutch rabbits were given oral administration of Tribufos at doses of 0, 1, 3, or 9 mg/kg/ day during gestation days 7 through 19. For cholinesterase inhibition, the LOEL was 1 mg/kg/ day based on inhibition of plasma and red blood cell cholinesterase activity; a NOEL was not established for this marker. For maternal systemic toxicity, the NOEL was 3 mg/kg/day and the LOEL was 9 mg/kg/day based on significantly decreased mean body weight gain. For developmental toxicity, the NOEL was ≥ 9 mg/kg/day (HDT); a LOEL was not established (MRID No. 40190602).

3. Reproductive Toxicity

- In a two-generation reproduction study, Sprague-Dawley rats were fed diets containing Tribufos at 0, 4, 32 or 260 ppm (0, 0.2, 1.7, or 15 mg/kg/day, respectively) for two successive generations. There was no increased sensitivity of pups over the adults. The parental systemic LOEL was 4 ppm (0.2 mg/kg/day) based on inhibition of plasma cholinesterase activity; a parental systemic NOEL was not established. For reproductive toxicity, the NOEL was 32 ppm (1.7 mg/kg/day) and the LOEL was 260 ppm (15 mg/kg/day) based on: 1) significant increases in the number of litters with stillborn pups and pup death (including cannibalism) throughout lactation; 2) decreases in F_1 and F_2 pup body weights, and; 3) significant increase in the F_1 gestation period (MRID No. 42040101).

4. Cholinesterase Inhibition

- In the developmental toxicity studies, cholinesterase activity was measured in adults but not in the pups, thus a comparisons could not be made on the effect of Tribufos in this biomarker.

- In the two-generation reproduction study, a comparison of the doses at which cholinesterase inhibition occurred in adults (0.2 mg/kg/day) versus pups (1.7 mg/kg/day) indicate that the pups may be less sensitive than adults to the cholinesterase-inhibiting effects of Tribufos.

5. Developmental Neurotoxicity

- The Committee determined that a developmental neurotoxicity study is *required.* The concern for the developmental neurotoxic potential of Tribufos was elicited by the following factors:

    1). Neuropathological lesions were observed in white leghorn hens following dermal exposure. Repeated dermal applications of Tribufos at 42 mg/kg/day for 90 days resulted in increased incidence of neuropathy of the central nervous system, particularly axonal degeneration in the brain.

    2). In the combined chronic toxicity/ carcinogenicity study in Fischer 344 rats dietary administration of Tribufos resulted non-statistically significant increases in retinal atrophy at 4 ppm (0.2 mg/kg/day) and 40 ppm (1.8 mg/kg/day in males and 2.3 mg/kg/day in females) as well as statistically significant increases in retinal atrophy in both sexes at 320 ppm (16.8 mg/kg/day in males and 21.1 mg/kg/day in females). Also seen at 360 ppm were posterior (subcapsular or complete cataract) lens opacity, corneal neovascularization, diffuse or focal corneal opacity, iritis and/or uveitis, and optic nerve degeneration.

    3). The lack of acute and subchronic neurotoxicity studies in rats (i.e., no measurement of functional deficit as well as histopathological evaluation of perfused tissues of the nervous system).

6. Data Gaps

Acute Neurotoxicity - Rat (§81-8)

Subchronic Neurotoxicity - Rat (§ 82-5)

C. CONCLUSIONS: HIARC's conclusions on the Uncertainty Factors for acute and chronic dietary as well as occupational/residential risk assessments are as follows:

1. Acute Dietary Risk Assessment

For acute dietary risk assessment, the Toxicology Endpoint Selection Committee selected the Maternal NOEL of 1 mg/kg/day based on inhibition of plasma and red blood cell cholinesterase activity at 7 mg/day (LOEL) in pregnant rats given oral administrations of Tribufos at 0, 1, 7 or 28 mg/kg/day during gestation days 6 through 16.

For acute dietary risk assessment, HIARC determined that the **10 x** factor to account for enhanced sensitivity of infants and children **(as required by FQPA) should be retained and thus a MOE of 1000 is required**. Although no increased sensitivity of fetuses as compared to maternal animals were observed following *in utero* exposure in developmental toxicity studies and no increased sensitivity of pups as compared to adults were observed in a multigeneration reproduction study, the Committee determined that **a MOE of 1000 is required** because:

(i) There are data gaps for acute and subchronic neurotoxicity studies. Because of these data gaps, data on measurement of cholinesterase inhibition and functional deficit as well as histopathological evaluation of perfused tissues of the nervous system are not available for evaluation.

(ii) There is evidence of neuropathological lesions (increased incidence of neuropathy of the central nervous system, particularly axonal degeneration in the brain) in white leghorn hens following dermal exposure.

(iii) There is concern for the developmental neurotoxic potential of Tribufos. This is based on the evidence of neuropathological lesions in the subchronic study with hens and in the combined chronic toxicity/carcinogenicity study in rats.

2. Chronic Dietary Risk Assessment

For chronic dietary risk assessment, the RfD/Peer review Committee selected a NOEL of 0.1 mg/kg/day based on inhibition of plasma cholinesterase activity at 0.4 mg/kg/day (LOEL) in both sexes of dogs given oral administrations of Tribufos at 0.1, 0.4 or 2 mg/kg/day for 52 weeks.

For chronic dietary risk assessment, the HIRAC determined that the **10 x** factor to account for enhanced sensitivity of infants and children **(as required by FQPA) should be retained for a total UF of 1000** (i.e.,10 x for inter-species variation, 10 x for intra-species variation and 10 x for FQPA). **Therefore, the RfD is revised as at 0.0001 mg/kg/day.** Although no increased sensitivity of fetuses as compared to maternal animals were observed following *in utero* exposure in developmental toxicity studies and no increased sensitivity of pups as compared to adults were observed in a multigeneration reproduction study, the UF of 1000 is supported by the following factors:

(i) There are data gaps for acute and subchronic neurotoxicity studies in rats. Because of these data gaps, data on measurement of cholinesterase inhibition and functional deficit as well as histopathological evaluation of perfused tissues of the nervous system are not available for evaluation.

(ii) There is evidence of neuropathological lesions (increased incidence of neuropathy of the central nervous system, particularly axonal degeneration in the brain) in white leghorn hens following dermal exposure.

(iii) There is concern for the developmental neurotoxic potential of Tribufos. This is based on the evidence of neuropathological lesions in the subchronic study with hens and in the combined chronic toxicity/carcinogenicity study in rats.

3. Occupational Exposure Dermal Risk Assessment

Tribufos is registered for use only in cotton. There are no registered residential uses at the present time. Therefore, doses, endpoints and MOEs are applicable only for occupational (dermal and inhalation) exposure risk assessments.

For Short-and Intermediate Term dermal risk assessments, the TESC selected a LOEL of 2 mg/kg/day (the lowest dose tested) based on dose-dependent inhibitions of plasma, erythrocyte and brain cholinesterase activity in rabbits following 15 repeated dermal applications of Tribufos at 0, 1, 10 or 25 mg/kg/day. This dose was supported by the LOEL of 2.6 mg/kg/day in the 90-day dermal toxicity study in hens.

TESC recommended the application of an additional Uncertainty Factor of 10 for the use of a LOEL for risk assessment (i.e. the lack of a NOEL in the critical study). HIARC concurred with TESC and determined that **a MOE of 1000 is required.** The additional UF of 10 is applied for FIFRA and not for FQPA. Becuase of the severity of the effect and the lack of a NOEL, a UF of 10 is applied instead of a 3 x factor. FQPA is not applicable since there are no registered residential use for Tribufos and thus infants and children are not exposed to Tribufos.

For **Long-Term dermal risk assessment**, the TESC determined that based on the current use pattern, Long-Term exposure is not anticipated. However, if the use pattern changes along with exposure, then the TESC recommended that the NOEL of 0.1 mg/kg/day established in the chronic dog study should be used for this risk assessment. **A MOE of 100 is** adequate because: 1) a NOEL was used for risk assessment and 2) FQPA is not applicable since there are no registered residential use for Tribufos and thus infants and children are not exposed to Tribufos.

For Short-, Intermediate- and Long-Term Inhalation risk assessments, the TESC determined that based on the current use pattern and exposure scenario, inhalation risk assessment is not required. However, if either of these conditions changes in the future, then TESC recommended that the NOEL of 2.43 mg/L (0.9 mg/kg/day) established in the 90-day inhalation study in rats should be used for this risk assessment. **A MOE of 100 is** adequate because 1) a NOEL was used for risk assessment and 2) FQPA is not applicable since there are no registered residential use for Tribufos and thus infants and children are not exposed to Tribufos.