7-14-97

DATE STAMPED: 07/14/97

MEMORANDUM DEF

SUBJECT: RfD/Peer Review Report of Tribufos {S,S,S-Tributyl phosphorotrithioate}

CASRN: 78-48-8
EPA Chem. Code: 074801
Caswell No.: 864

FROM: George Z. Ghali, Ph.D.
Manager, RfD/QA Peer Review Committee
Health Effects Division (7509C)

THRU: William Burnam
Chairman, RfD/QA Peer Review Committee
Health Effects Division (7509C)

TO: Philip Errico, PM 25
Insecticide-Rodenticide Branch
Registration Division (7505C)

Chief, Reregistration Branch
Special Review and Reregistration Division (7508W)

The Health Effects Division-RfD/Peer Review Committee met on January 23, 1997 to discuss and evaluate the existing and/or recently submitted toxicology data in support of Tribufos (DEF) reregistration and to reassess the Reference Dose (RfD) for this chemical.

Material available for review consisted of data evaluation records (DERs) for a combined chronic toxicity/carcinogenicity study in rats **(83-1a and -2a)**, a chronic toxicity study in dogs **(83-1b)**, a carcinogenicity study in mice **(83-2b)**, reproductive toxicity studies in rats **(83-4)**, developmental toxicity studies in rats **(83-3a)** and rabbits **(83-3b)**, a subchronic dermal delayed neurotoxicity study in hens **(82-7)**, and a battery of mutagenicity studies **(84-2)**.

A. Chronic and Subchronic Toxicity:

I. Chronic Toxicity in Rats:

The Committee considered the chronic toxicity phase (83-1a) of the combined chronic toxicity/carcinogenicity study in rats (83-5, MRID No. 42335101) to be acceptable and the data evaluation record (HED Doc. No. 0101119) to be adequate.

In this study, the chemical was tested in the Fischer 344 rat at dietary levels of 4, 40 and 320 ppm (equivalent to 0.2, 1.8 and 16.8 mg/kg/day in males; and 0.2, 2.3 and 21.1 mg/kg/day in females). The LOEL for plasma cholinesterase inhibition in both sexes was 4 ppm (0.2 mg/kg/day), the lowest dose level tested. The NOEL/LOEL for red blood cell cholinesterase inhibition in both sexes were 4 ppm (0.2 mg/kg/day for both males and females) and 40 ppm (1.8 and 2.3 mg/kg/day, in males and females, respectively). The NOEL/LOEL for brain cholinesterase inhibition in both sexes were 40 and 320 ppm, respectively.

The systemic toxicity NOEL/LOEL were established at 4 and 40 ppm, respectively, based on decreased weight gain, cholesterol and calcium in males; decreased red blood cell count, hemoglobin, and hematocrit in both sexes. Posterior (subcapsular or complete cataract), lens opacity, corneal neovascularization, diffused or focal corneal opacity, iritis and/or uveitis, and optic nerve degeneration were observed in both sexes of the 320 ppm group (16.8 and 21.1 mg/kg/day in males and females, respectively).

II. Chronic Toxicity in Dogs:

The Committee considered the chronic toxicity study in dogs (83-1b, MRID No. 42007203) to be acceptable and the data evaluation record (HED Doc. No. 42007203) to be adequate.

In this study, the test material was administered orally to beagle dogs at the dose levels of 4, 16 or 64 ppm (equivalent to 0.1, 0.4, and 1.7 mg/kg/day in males; 0.1, 0.4, and 2.0 mg/kg/day in females). Inhibition of plasma cholinesterase was observed in both sexes at the mid- (16 ppm) and high dose (64 ppm) levels. Inhibition of erythrocyte cholinesterase was observed in both sexes at the high dose level. A possible decrease in erythrocyte count was observed in both sexes at 64 ppm. No other treatment-related effects were observed. The NOEL/LOEL for plasma cholinesterase inhibition were 4 and 16 ppm (0.1 and 0.4 mg/kg/day, respectively, in both males and females). The NOEL/LOEL for erythrocyte cholinesterase inhibition were 16 and 64 ppm (0.4 mg/kg/day in both males and females, and 1.7 and 2.0 mg/kg/day in males and females, respectively). The NOEL for brain cholinesterase inhibition was 64 ppm (1.7 mg/kg/day in males and 2.0 mg/kg/day in females), the highest dose level tested.

III. Chronic Toxicity in Mice:

The Committee examined the chronic toxicity phase of the mouse carcinogenicity study (83-2b, MRID No. 41171001, 40611301, HED Doc. No. 007802). In this study, the test chemical was administered to CD-1 mice at dietary levels of 10, 50 or 250 ppm (equivalent to 1.64, 8.28, and 48.02 mg/kg/day in males; 2.08, 11.14, and 63.04 mg/kg/day in females) for 90 weeks.

The LOEL for plasma and red blood cell cholinesterase inhibition for both sexes, and for brain cholinesterase inhibition in males was established at 10 ppm (1.64 mg/kg/day in males, and 2.08 mg/kg/day in females). The NOEL/LOEL for brain cholinesterase inhibition in females were established at 50 ppm (11.14 mg/kg/day) and 250 ppm (63.04 mg/kg/day).

The NOEL/LOEL for systemic toxicity for both sexes were 10 ppm (1.64 mg/kg/day in males, and 2.08 mg/kg/day in females), and 50 ppm (8.28 mg/kg/day in males, and 11.14 mg/kg/day in females). At 50 ppm, an increased number of males showed paleness and hunched backs. At 78 weeks males showed decreased MCV and MCH and at week 90 decreased MCH. At week 90 females showed decreased RBC count, hemoglobin and hematocrit. Histopathology of the males showed; adrenal amyloidosis, epididymal hyperspermatogenensis, small intestinal amyloidosis and vacuolar degeneration of the epithelium, and splenic hematopoiesis.

IV. Subchronic Toxicity:

There were no subchronic oral toxicity studies (82-1a or -1b) available for review by the Committee at the time of the meeting. For the purpose of less-than life time risk assessment and based on the exposure profile established for Tribufos, the Committee recommended that a 21-day dermal toxicity study including measurements of cholinesterase inhibition at different intervals be submitted.

However, subsequent to the meeting, it was found that a 21-day dermal toxicity study in rabbits (82-2, 1991, MRID No. 42007201, HED Doc. No. 010118) was available. According to the scientific reviewer, the study was acceptable.

In this study, Tribufos was tested at nominal dose levels of 2, 11, 29 mg/kg/day (actual dose levels 2, 11, 29 mg/kg/day). The test chemical was applied six hours per day, five days per week.

The data evaluation record states that at 29 mg/kg/day, one male and four females died or were sacrificed in extremis. Signs of systemic toxicity and mild or moderate dermal irritation were observed in both sexes in the mid- and high-dose groups. In males, plasma cholinesterase inhibition occurred at 2 mg/kg/day and higher dose levels; a NOEL was not established. In females, the NOEL/LOEL

for plasma cholinesterase inhibition were established at 2 and 11 mg/kg/day, respectively. In males, the NOEL/LOEL for erythrocyte cholinesterase inhibition were established at 2 and 11 mg/kg/day, respectively. In females, erythrocyte cholinesterase inhibition occurred at 2 mg/kg/day and higher dose levels; a NOEL was not established. In both sexes, the NOEL/LOEL for brain cholinesterase inhibition were 2 and 11 mg/kg/day, respectively,

B. Carcinogenicity:

The Committee did not discuss the carcinogenicity phase (83-2a) of the combined chronic toxicity/carcinogenicity study in rats (83-5, MRID No. 42335101, HED Doc. No. 0101119) or the carcinogenicity phase of the chronic feeding/carcinogenicity study in mice (83-2b, MRID No. 41171001, 40611301, HED Doc. No. 007802). The carcinogenicity issue had already been addressed and the carcinogenic potential had been classified by the Health Effects Division-Carcinogenicity Peer Review Committee (HED-CPRC) in the meeting of January 8, 1997.

"In accordance with the EPA proposed Guideline for Carcinogenic Risk Assessment (April 10, 1996), Tribufos was characterized as "likely" at high doses and "unlikely" at low doses, based on increases in multiple tumor types in both sexes of the CD-1 mouse only at the highest dose, which were accompanied by severe toxicity at multiple endpoints. A linear risk assessment based on the tumors was not recommended, because of the severe accompanying toxicity, typical of many organophosphorus chemicals; therefore a non-linear approach (Margin of Exposure or MOE) using the most sensitive toxic endpoint was recommended" (HED-CPRC draft report March 3, 1997).

C. Reproductive and Developmental Toxicity:

I. Reproductive Toxicity:

The Committee considered the 2-generation reproductive toxicity study in rats (83-4, 1991, MRID No. 42040101) to be acceptable and the data evaluation record (HED Doc. No. 009140) to be adequate, with revisions of the pup systemic NOEL/LOEL and to the Executive Summary.

The chemical was tested in Sprague-Dawley rats at dietary levels of 4, 32, or 260 ppm (approximately 0.2, 1.7, or 15 mg/kg/day). The adult systemic LOEL was 4 ppm (0.2 mg/kg/day), the lowest dose level tested, based on decreased plasma cholinesterase. At 32 ppm (1.7 mg/kg/day), body weight and food consumption were reduced throughout the lactation period; red blood cell and/or brain cholinesterase were inhibited at 32 and 260 ppm. The pup systemic NOEL/LOEL were set by the Committee at 4 ppm (0.2 mg/kg/day) and 32 ppm (1.7 mg/kg/day) based on decreased plasma cholinesterase in 21-day old F1 females. At 260 ppm (15

mg/kg/day), red blood cell and brain cholinesterase were inhibited, particularly in F2 pups of both sexes. The reproductive toxicity NOEL/LOEL were 32 ppm (1.7 mg/kg/day) and 260 ppm (15 mg/kg/day), based on a significant increase in the number of litters with stillborn pups and in pup deaths (including cannibalism) throughout lactation, decreased pup F1 and F2 body weights, and a significant increase in the gestation period for F1 females.

The Committee considered the cross-fostering reproduction study in rats (Non-Guideline, 1991, MRID 2040103) to be acceptable and the data evaluation record (HED Doc. No. 009140) to be adequate with revision to the Executive Summary format.

The chemical was tested in Sprague-Dawley rats at a dietary level of 260 ppm (approximately 15 mg/kg/day). This study was conducted to determine if pup loss (death plus cannibalism) observed in the previous study (MRID No. 42040101) was due to treatment of dams, pups *in utero*, or both. Treatment of dams consisted of dietary administration for 10 weeks premating and during mating/gestation/lactation. The observed order of sensitivity (high to low), as measured by pup death, was: treated pups fostered to treated dams, untreated pups fostered to treated dams, treated pups fostered to untreated dams, and untreated pups fostered to untreated dams. A synergistic effect of maternal and *in utero* exposures to tribufos was demonstrated. The data showed that pup mortality was higher in the test group comprised of treated dams fostering untreated pups than in the group comprised of untreated dams fostering treated pups, and suggested that the maternal treatment may have contributed more than the *in utero* exposure of the pups to the observed pup death. Confirmatory plasma and red blood cell cholinesterase inhibition was observed in the dams at week 9 of treatment and at termination for the groups with treated dams; maternal brain cholinesterase inhibition was also seen at termination. There were no cholinesterase measurements prenatal for any of the pups.

The Committee considered the fertility study of F1 rats (Non-Guideline, 1991, MRID 42040102) to be unacceptable and the data evaluation record (HED Doc. No. 009140) to be adequate with some revisions (Executive Summary).

The chemical was tested in Sprague-Dawley rats at a dietary level of 260 ppm (approximately. 15 mg/kg/day). This study was conducted to determine effects on fertility in cross-fostered F1 pups from the previous supplementary study (MRID 42040103). The groups consisted of untreated pups (which had been cross fostered to untreated dams) and treated pups (which had been cross fostered to treated dams). After 10 weeks of treatment, there was no apparent effect on fertility in the treated group. No other reproductive parameters were examined, but the cholinesterase inhibiting effects of the test substance were confirmed. Due to an

error during the study resulting in animals being given mixed test feed for one day during the mating period, the study was considered to be unacceptable by the Committee; however this study was not considered to be critical to the registration process or to the interpretation of the reproductive toxicity of tribufos.

II. Developmental Toxicity

The Committee considered the developmental toxicity study in rats (83-3a, 1987, MRID No. 92034005) to be acceptable and the data evaluation record (HED Doc. No. 007802) to be adequate with revision to the Executive Summary format.

The chemical was administered by gavage to Sprague-Dawley rats at the dose levels of 1, 7, or 28 mg/kg/day on gestation days 6-15. The maternal NOEL/LOEL were 1 and 7 mg/kg/day, based on decreased red blood cell and plasma cholinesterase activity. At 28 mg/kg/day, brain cholinesterase was also depressed and mean weight gain was significantly decreased. The developmental toxicity NOEL was $\geq$28 mg/kg/day, the highest dose level tested. There was no effect on brain cholinesterase in day 20 fetuses; gestation day 20 was the only time point when fetal cholinesterase was measured.

The Committee considered the developmental toxicity study in rabbits (83-3b, 1987, MRID No. 40190602, 92034006) to be acceptable and the data evaluation record (HED Doc. No. 007802) to be adequate.

The chemical was administered by gavage to American Dutch rabbits at the dose levels of 1, 3, or 9 mg/kg/day on gestation days 7-19. The maternal cholinesterase LOEL was 1 mg/kg/day, the lowest dose level tested, based on decreased red blood cell and plasma cholinesterase activity. The maternal systemic toxicity NOEL/LOEL were 3 and 9 mg/kg/day, based on significantly decreased mean weight gain. The developmental NOEL was $\geq$9 mg/kg/day, the highest dose level tested.

III. Developmental Neurotoxicity:

The Committee determined that insufficient information is available at this time to fully support a recommendation for a developmental neurotoxicity study in rats. The Committee further recommended that the need for this study should be reconsidered when additional applicable data, such as acute or chronic neurotoxicity studies in rats, are submitted to the Agency. Concern for the developmental neurotoxic potential of Tribufos was elicited by evidence of neurohistopathological lesions which were observed in two studies submitted in support of tribufos registration:

1. Increased incidence of neuropathy of the central nervous system, particularly axonal degeneration in the brain, was observed

after 13 weeks of daily application (5 days/week) of tribufos to the comb at a dose of 42 mg/kg/day in a subchronic delayed neurotoxicity study in white leghorn hens.

2. Retinal atrophy was observed in both males and females at statistically significant incidences after 2 years of dietary administration at 320 ppm (16.8 mg/kg/day in males, and 21.1 mg/kg/day in females) in a combined chronic toxicity/oncogenicity study in Fischer 344 rats. Nonsignificant incidences of retinal atrophy were also observed at 4 (0.2 mg/kg/day) and 40 ppm (1.8 mg/kg/day in males and 2.3 mg/kg/day in females). Signs of retinal degeneration were evident at the 12-month interim sacrifice.

It cannot be determined whether the primary endpoints examined in the developmental neurotoxicity study in rats would provide additional information. There is insufficient evidence to determine whether the rat is an appropriate animal model for a developmental neurotoxicity study.

Neither an acute nor a subchronic neurotoxicity study has been conducted with tribufos, and neurotoxicology endpoints recorded for other studies were negative. The following categories of endpoints, which are required or could be examined in the developmental neurotoxicity study, were considered:

1. Structural developmental anomalies: No treatment-related incidences of CNS anomalies were observed in either the prenatal developmental toxicity study in rats or rabbits.

2. Functional deficits: No measurements of functional deficit, such as those which might be evaluated on an acute and/or subchronic neurotoxicity study in rats, have been studied following administration of tribufos.

3. Neuropathology: An adequate evaluation of the neuropathology of tribufos exposure has not been conducted, since histopathological evaluation of perfused tissues of the nervous system, which is required for acute and subchronic neurotoxicity studies, has not been performed. Other studies that have been conducted on tribufos, but which did not require perfusion techniques, have demonstrated no neuropathology. For example, no histopathological lesions of the brain or peripheral nervous system were observed in the subchronic or chronic toxicity studies in rodents, and brain weight values which were measured on the chronic rat study were not affected by treatment.

4. Biomarkers of exposure: Following the treatment of adult rats with Tribufos, their offspring demonstrated a reduced response to the maternally-mediated treatment, as measured by cholinesterase inhibition.

D. Neurotoxicity:

There were no acute or subchronic neurotoxicity studies in rats available for review by the Committee. The Committee determined that these studies are required.

The Committee considered the subchronic delayed neurotoxicity study in hens (82-7, 1991, MRID No. 42007202) to be acceptable and the data evaluation record (HED Doc. No. 009579) to be adequate.

The chemical was administered via the dermal route over a period of 90 day to hens at dose levels of 2.6, 11 or 42 mg/kg/day. A positive control, Tri-orthocresol phosphate (TOCP), was included administered at a dose level of 18 mg/kg/day. The test material was applied to he comb of the hen. The systemic toxicity NOEL/LOEL were 2.6 and 11 mg/kg/day, respectively, based body weight gain decrease. Whole blood cholinesterase inhibition was observed at 2.6 mg/kg/day, the lowest dose level tested. Histopathological changes indicative of neurotoxicity were observed primarily in the brain and spinal cord. The NOEL/LOEL for neurotoxicity is 11 and 42 mg/kg/day, respectively, based on the histopathological changes of the brain and spinal cord.

E. Mutagenicity:

Three acceptable mutagenicity studies (84-2) were available for review by the Committee. The following is a summary of these studies and Committee's conclusions for each study:

I. Gene Mutation:

Salmonella typhimurium reverse gene mutation assay (MRID No. 41459101, HED Doc. No. 007996): The test was negative in strains TA1535, TA1537, TA1538, TA98 and TA100 up to the HDT (10,000 μg/plate +/- S9).

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II. Chromosomal Aberrations:

In vitro cytogenetic assay in Chinese hamster ovary (CHO) cells (MRID NO. 41459103, HED Doc. No. 007996). The test was negative up to cytotoxic concentrations (≥0.025 μL/mL -S9; ≥0.05 μL/mL +S9).

III. Other Mutagenic Mechanisms:

In vitro unscheduled DNA synthesis (UDS) in primary rat hepatocytes assay (MRID NO. 41459102, HED Doc. No. 007996). The test was negative up to the HDT (0.006 μL/mL). Higher levels (≥0.01 μL/mL) were severely cytotoxic.

IV. Other Information:

The limited open literature information available on the mutagenicity of this chemical confirmed that tribufos is not genotoxic.

V. Conclusions (Mutagenicity):

Overall, the Committee concluded that the acceptable studies satisfy the pre-1991 mutagenicity initial testing battery guidelines. Based on the findings of the acceptable studies, there is no concern for mutagenicity at this time.

F. FQPA Considerations:

Under the directive of the Food Quality Protection Act (FQPA) recently enacted as an amendment to the Federal-Fungicide-Insecticide-Rodenticide Act (FIFRA), the Committee examined the data to assess any extra sensitivity for infants and children, and determined that:

1. The data base included an acceptable two-generation reproduction study in rats and acceptable prenatal developmental toxicity studies in rats and rabbits, meeting the basic data requirements for a food-use chemical, as defined by 40 CFR Part 158.

2. The data provided no indication of increased sensitivity of rats or rabbits to *in utero* and/or postnatal exposure to Tribufos. On the contrary, the data appear to indicate that the offspring may actually be less sensitive to treatment, as mediated by maternal exposure, than are the adults. This conclusion was based on the following observations:

a. In the two-generation reproduction study in rats, a comparison of the doses at which ChE was inhibited in adults (4 ppm; 0.2 mg/kg/day) versus pups (32 ppm; 1.7 mg/kg/day), indicates that pups may be less sensitive than adults to the cholinesterase-inhibiting effects of tribufos.

b. In a cross-fostering study in rats, pup mortality was higher in the test group comprised of treated dams fostering untreated pups than in the group comprised of untreated dams fostering treated pups. This suggests that the maternal treatment may have contributed more than the *in utero* exposure of the pups to the observed pup death.

c. In both the prenatal developmental toxicity studies in rats and rabbits, developmental toxicity was not observed, although the doses administered produced evidence of cholinesterase

inhibition and other signs of systemic toxicity in the maternal animals.

d. Similar findings (cholinesterase inhibition in dams in the absence of developmental toxicity or brain cholinesterase inhibition in day 20 fetuses) were reported in the open literature in a study by Astroff et al. (1996). In this study, six organophosphorus compounds, including azinphos-methyl, fenamiphos, fenthion, isofenphos, oxydemeton-methyl, and tribufos, were administered to Sprague-Dawley rats during gestation days 6-15.

G. Reference Dose (RfD):

The Committee recommended that an RfD for this chemical be established on the chronic toxicity study in the dog with a NOEL of 0.1 mg/kg/day. In this study, the NOEL/LOEL for plasma cholinesterase inhibition were 4 and 16 ppm (0.1 and 0.4 mg/kg/day, respectively, in both males and females). The NOEL/LOEL for erythrocyte cholinesterase inhibition was 16 and 64 ppm (0.4 mg/kg/day in both males and females, and 1.7 and 2.0 mg/kg/day in males and females, respectively). The NOEL for brain cholinesterase inhibition was 64 ppm (1.7 mg/kg/day in males and 2.0 mg/kg/day in females), the highest dose level tested.

The Committee recommended that the chronic and reproductive toxicity studies in rats be used as co-critical studies along with the chronic toxicity study in dogs.

An Uncertainty Factor (UF) of 100 was applied to account for both the interspecies extrapolation and intraspecies variability. On this basis the RfD was calculated to be 0.001 mg/kg/day.

The data provided no indication of increased sensitivity of rats or rabbits to *in utero* and/or postnatal exposure to Tribufos. Therefore, the use of an additional Safety Factor for the protection of infants and children was not warranted.

It should be noted that this chemical has not been reviewed by the WHO/FAO Joint Meeting of Pesticide Residues and an Acceptable Daily Intake (ADI) has not been established for this chemical.

H. Data Gaps and Other Data Requirements:

The Committee determined that insufficient information is available at this time to fully support a recommendation for a developmental neurotoxicity study in rats. The Committee further recommended that the need for this study should be reconsidered when additional applicable data, such as acute or chronic neurotoxicity studies in rats, are submitted to the Agency. Concern for the developmental neurotoxic potential of Tribufos was elicited by evidence of neurohistopathological lesions which were

observed in two studies submitted in support of tribufos registration described earlier.

I. Individuals in Attendance:

Peer Review Committee members and associates present were William Burnam (Chief, SAB; Chairman, RfD/Peer Review Committee), George Ghali (Manager, RfD/Peer Review Committee), Karl Baetcke (Chief, TB I), Mike Ioannou (Acting Chief, TB II), Marion Copley, Susan Makris, Nancy McCarroll, Kit Farwell, Guruva Reddy, Henry Spencer, and Rick Whiting. In attendance also was Jane Smith of HED as an observer.

Scientific reviewers (Committee or non-committee member(s) responsible for data presentation; signature(s) indicate technical accuracy of panel report):

Robert Zendzian _____

Respective Branch Chief (Committee member; signature indicates concurrence with the peer review unless otherwise stated)

William Burnam _____

CC: Stephanie Irene
Debra Edwards
William Burnam
Robert Zendzian
Karen Whitby
Amal Mahfouz (OW)
RfD File
Caswell File

J. Material Reviewed:

1. Christenson, W. (1992). Technical Grade Tribufos (DEF): A Chronic Toxicity/Oncogenicity/Neurotoxicity Feeding Study in the Fisher 344 Rat. MRID No. 42335101. HED Doc. 010119. Classification: Core Guideline.

2. Hayes, R. (1988). Oncogenicity Study of Technical Grade Tribufos (DEF) with Mice. MRID No. 41171001, HED Doc. No. 007802. Classification: Core Guideline.

3. Christenson, W. (1991). Chronic Feeding Toxicity Study of Technical Grade Tribufos (DEF) with Dogs. MRID No. 42007203. HED Doc. No. 009579. Classification: Core Guideline.

4. Eigenberg, D. and Elcock, L. (1991). A Two-Generation Reproduction Study in Rats Using Tribufos (DEF). MRID No. 42040201. HED Doc. No. 009140. Classification: Core Guideline.

5. Eigenberg, D. A. (1991). A cross fostering study in rats using Tribufos (DEF). MRID No. 42040103, HED Doc. No. 009140. Classification: Acceptable.

6. Eigenberg, D. A. (1991). A dietary reproductive toxicity study investigation of the fertility of F1 rats using Tribufos (DEF). MRID No. 42040102, HED Doc. No. 009140. Classification: Unacceptable.

7. Kowalski, R. (1986). A Teratology Study with DEF Technical in the Rat. MRID No. 40190601. HED Doc. No. 007802. Classification: Core Guideline.

8. Clemens, G. et al. (1987). Teratology Study in the Rabbit with DEF Technical. MRID No. 40190602. HED Doc. No. 007802. Classification: Core Guideline.

9. Sheets, L. (1991). Subchronic Delayed Neurotoxicity Study with Technical Grade Tribufos (DEF) in Hens. MRID No. 42007202. HED Doc No. 009579. Classification: Core Guideline.

10. Sheets, L. P. and Phillips, S. D. (1991). 21-Day Dermal Toxicity Study with Technical Grade Tribufos (DEF) in Rabbits. MRID No. 42007201, HED Doc. No. 010118. Classification: Core Guideline.

11. Curren, R. and Gentry, P. (1989). Salmonella/Mammalian-microsome Plate Incorporation Mutagenicity Assay (Ames Test). MRID No. 41459101. HED Doc. No. 007996. Classification: Acceptable.

12. Curren, R. (1990). Unscheduled DNA Synthesis in Rat Primary Hepatocytes. MRID No. 41459102. HED Doc. No. 000000. Classification: Acceptable.

13. Putnam, D. and Morris, M. (1989). Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells. MRID No. 41459103. HED Doc. No. 000000. Classification: Acceptable.

K. References Cited:

1. Astroff, A.B., G.K. Sangha, and J.H. Thyssen. (1996) The relationship between organophosphate-induced maternal cholinesterase inhibition and embryo-fetal effects in the Sprague-Dawley rat. *Toxicologist* 30:191.