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

013709

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

DATE: **August 31, 1999**

MEMORANDUM

SUBJECT: ***EPTC*** - REVISED Report of the Hazard Identification Assessment Review Committee.

FROM: Robert F. Fricke
Reregistration Branch 2
Health Effects Division (7509C)

THROUGH: Jess Rowland, Co-Chair 9/1/99
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)
and
Pauline Wagner, Co-Chair 9/1/99
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Alan Nielsen, Branch Senior Scientist
Reregistration Branch II
Health Effects Division (7509C)

PC Code: 041401

On September 17, 1998, the Health Effects Division's Hazard Identification Assessment Review Committee (HIARC) evaluated the toxicological endpoints selected for acute and chronic dietary for **EPTC**, as well as the occupational and residential (dermal and inhalation) exposure risk assessments. The HIARC also addressed the potential enhanced sensitivity of infants and children from exposure to EPTC as required by the Food Quality Protection Act (FQPA) of 1996. The Committee's conclusions were presented in a report dated October 23, 1998 (HED Doc No.: 012922).

On July 29, 1999 the HIARC reconsidered the short- and intermediate-term inhalation endpoints selected for occupational and residential exposure risk assessments based on the re-evaluation of the 90-day inhalation toxicity study in rats (MRID No. 00154784).

Committee Members in Attendance

Members present were: William Burnam, Virginia Dobozy, Karen Hamernik, Pamela Hurley, Susan Makris, Nancy McCarroll, Jess Rowland, PV Shah, and Brenda Tarplee (Executive Secretary).

Also in attendance were: Paula Deschamp, RRB2.

Data Presentation:
and
Robert F. Fricke

Robert F. Fricke

Toxicologist

I. INTRODUCTION

EPTC was reviewed by the Health Effects Division (HED) Hazard Identification Assessment Committee (HIARC) on September 1 and October 13, 1998. The HIARC evaluated the toxicological endpoints for acute and chronic dietary as well as occupational and residential (dermal and inhalation) exposure risk assessments. The HIARC also addressed the potential susceptibility of infants and children as required by the Food Quality Protection Act (FQPA) of 1996.

The HIARC met again on July 29, 1999 to discuss the short and intermediate inhalation endpoints for use in risk assessment.

This report includes the decisions made at the July 29, 1999 HIARC meeting as well as those made by the previous HIARC and RfD Committee meetings and thus supersedes the previous HIARC report of October 23, 1998 and the RfD Committee report of Oct 28, 1986.

II. HAZARD IDENTIFICATION

A. Acute Dietary Reference Dose (RfD)

Type of Study: Acute Neurotoxicity Study in the Rat: 870.6200 (§81-8)

MRID Nos.: 43039701 and 43297401

Executive Summary: In an acute neurotoxicity study in Alpk:APfSD rats (10/sex/dose, 34 to 36 days old) were treated orally with EPTC (98.4%) at doses of 0 (vehicle only, 100% corn oil), 200, 1000, or 2000 mg/kg (MRID Nos.: 43039701, 43297401). Clinical observations were made at least once daily, while body weights, Functional Observational Battery (FOB) and motor activity were evaluated at prestudy, at the peak time of effect (5 hr post-dosing) and on days 8 and 15. At study termination, five animals/sex/dose were perfusion fixed for neurohistopathological evaluation. Four animals died or were euthanized within two days post-dosing; two high-dose males were found dead on day 2, and one female each from the mid-dose and high-dose groups were sacrificed *in extremis* on days 1 and 2, respectively. Body weights were reduced in mid- and high-dose males on day 8 (5.9 and 15.6%, respectively) and day 15 (2% and 9%, respectively). Body weights of high-dose females were significantly lower (4%) than control values on day 8, but were slightly higher than control values by day 15. Food consumption was reduced during the first week treatment in mid- and high-dose males (14% and 35%, respectively, $p \leq 0.01$).

Neurobehavioral evaluations (FOB and motor activity) revealed treatment-related effects at the peak time-of-effect (1 to 5 hr post-dosing) with decreasing incidence on subsequent days. Clinical signs were observed in mid- and high-dose animals at the peak time-of-effect (lacrimation, salivation, hypoactivity, upward curvature of the spine, and reduced foot withdrawal reflex). Some animals continued to show clinical signs on day 2; animals were, in general, symptom free on days 4 or 5. For the first five minutes post-dosing, decreased motor activity was observed in mid- and high-dose males and high-dose females; overall motor activity of treated animals was similar to control values.

Neuropathological evaluations revealed neuronal necrosis in pyriform/entorhinal cortex of the cerebrum or the ventral/caudal portion of the dentate gyrus or both in the brains of low- (males: 2/5, minimal; 0/5, females), mid- (males: 1/5, minimal, 3/5, slight, 1/5, moderate; females: 3/5, slight, 2/5, moderate) and high- (males: 5/5, marked; females: 2/5, moderate, 3/5, marked) dose animals. Based on the results of this study, a NOAEL in males was not established; the LOAEL was 200 mg/kg based on neuronal cell necrosis in the brain. In females, the NOAEL was 200 mg/kg and the LOAEL was 1000 mg/kg based on clinical signs, death, and neuronal cell necrosis in the brain.

Dose and Endpoint for Establishing Acute RfD: LOAEL = 200 mg/kg in males based on neuronal cell necrosis in the brain at the lowest dose tested.

Uncertainty Factor: 300 (10x for inter-species extrapolation, 10x for intra-species variability, and 3x for the use of LOAEL; lack of a NOAEL in the critical study).

$$\textbf{Acute RfD} = \frac{\textbf{200 mg/kg (LOAEL)}}{\textbf{300 (UF)}} = \textbf{0.67 mg/kg}$$

Comments about Study/Endpoint/Uncertainty Factors: This study is appropriate for acute dietary risk assessment since the effects were observed following a single exposure to EPTC. The endpoint selected (neuronal cell necrosis in the brain) is also appropriate since this neuropathological effect has been observed several other studies (subchronic neurotoxicity study in rats, chronic feeding study in the rat, and one-year oral (capsule) study in the dog). Since a NOAEL was not established for males and the LOAEL was used, an additional modifying factor of 3x was used in deriving the acute RfD.

The Registrant has submitted additional data (MRID No.: 43948301), which established new criteria for evaluating neuronal cell necrosis in the brain. Using this criteria, an addendum (MRID No.: 43964301) to the original acute neurotoxicity study was submitted to the Agency but has not been reviewed at this time. In this addendum, the neuronal lesions observed in low-dose (200 mg/kg) males were reclassified as not treatment-related and attributable to normal background incidence of this lesion. In this addendum, the NOAEL was reestablished as 200 mg/kg in males and females. However, **the committee recommended that the photomicrographs of the neuronal cell lesions in the brain be reevaluated by an independent pathologist to determine the validity of the of the new evaluation criteria and the reestablishment of the NOAEL to 200 mg/kg.** If the Registrant's reevaluation of the histopathology data has merit, then the committee recommend that the rabbit developmental toxicity study (MRID 40442302) be considered for establishing the acute dietary endpoint. Even though the committee felt that the neuronal cell necrosis was the better toxicological endpoint, some members of the committee felt that the decreased fetal pup weight observed in the rabbit developmental study could have been produced by a single oral dose of EPTC. The NOAEL for the rabbit developmental study was established at 40 mg/kg/day.

This risk assessment is required.

B. Chronic Dietary Reference Dose (RfD)

Type of Study: Two-generation reproduction study - rat 870.3800 (§83-4)

MRID No.: 00161597

Executive Summary: In this two-generation, two litter reproduction study, EPTC (98.4%) was administered to weanling (no age given) Crl:CD(SD)Br rats (30/sex/dose) at dietary levels of 0, 50, 200, or 800 ppm (calculated doses: 0, 2.5, 10, or 40 mg/kg/day). There were no treatment-related clinical findings. Morality occurred sporadically in all dose groups and was not suggestive of any treatment-related effect, further, post-mortem examination of these animals indicated that the deaths were incidental. At the high-dose level, body weights during the pre-mating period were statistically significantly ($p \leq 0.05$) decreased in F_0 males (6.5 to 12.1%, weeks 8 to 23) and females (9.2 to 8.5%, weeks 8 to 12), and in F_1 males (13 to 19.5%, weeks 0 to 23) and females (7.3 to 12.2%, weeks 0 to 12). Body weights were significantly decreased by 6.3 to 9.1% in F_0 females and 10.8 to 12.8% in F_1 females from GD 0 to 20. During lactation, body weights of F_0 females were decreased by 10.9% only on day 0, while that of F_1 females was decreased by 8.8 to 14.2% throughout the lactation period. Food consumption was significantly reduced during pretreatment high-dose F_0 males and low-, mid- and high dose F_1 males. Food consumption was reduced in high-dose F_1 females with sporadic decreased noted at the low- and mid-dose levels. During the first week of gestation, food consumption was decreased only in high-dose F_1 females.

Evaluation of clinical pathology parameters did not reveal any treatment-related changes; brain, plasma, and erythrocyte ChE activities of treated animals were comparable to control values. Post-mortem observations and gross necropsy findings of adult animals did not suggest any parental toxicity. Histological findings of F_0 tissues revealed only incidental findings. However, after weaning of the F_{2a} litters, the incidence of degenerative cardiomyopathy in F_1 adults was 4/25, 3/25, 15/25 and 25/25 in control, low-, mid- and high-dose males, respectively, and 1/25, 0/25, 5/25 and 25/25 control, low-, mid- and high-dose females, respectively; hearts were not examined in the F_0 animals. Mean body weights of F_{1a} and F_{1b} high-dose pups were statistically significantly ($p \leq 0.05$) in males (9.2 to 21%, weeks 0 to 21) and females (16 to 25%, weeks 4 to 21). No other treatment-related differences were noted in any of the other reproductive parameters.

For parental systemic toxicity, the NOAEL was 2.5 mg/kg/day and the .LOAEL was 10 mg/kg/day based on degenerative cardiomyopathy.

For developmental toxicity, the NOAEL was 10 mg/kg/day and the LOAEL was 40 mg/kg/day based on decreased mean pup weight during lactation days 4 to 21.

For reproductive toxicity, the NOAEL was 40 mg/kg/day (HDT); a LOAEL was not attained.

Dose for Establishing Chronic RfD: NOAEL = 2.5 mg/kg/day based on dose-related increases in the incidences of degenerative cardiomyopathy at 10 mg/kg/day (LOAEL) was established at of 2.5 mg/kg/day.

Uncertainty Factor(s): 100X (10x for inter-species extrapolation, and 10x for intra-species variability).

$$\textit{Chronic RfD} = \frac{\textit{2.5 mg/kg/day (NOAEL)}}{\textit{100 (UF)}} = \textit{0.025 mg/kg/day}$$

Comments about Study/Endpoint/Uncertainty Factors: The endpoint of concern (degenerative cardiomyopathy) is supported by the same endpoint observed in the combined 2-year chronic toxicity/carcinogenicity study in the rat (MRID No 40215001). In that study, increased incidence of degenerative cardiomyopathy was seen at the lowest dose tested (9 mg/kg/day); a NOAEL was not achieved. The use of the LOAEL (9 mg/kg/day) and UF of 300 (100x for inter-species extrapolation, 10x for intra-species variation, and an additional 3x for the use of a LOAEL) would result in an RfD of 0.03 mg/kg/day (i.e., 9 ÷300 = 0.03) which is comparable to that derived by the use of a NOAEL and a UF of 100 from the two-generation study as shown above.

Cardiomyopathy was also observed in other subchronic and chronic toxicity studies in the rat. In a chromic feeding/oncogenicity study (MRID Nos.: 00145004 and 00146311), a NOAEL was established at 5 mg/kg/day based on a increased incidence of cardiomyopathy observed in males dosed at the LOAEL of 25 mg/kg/day. Myocardial lesions were also observed at the LOAEL in subchronic feeding study in the rat (MRID No.: 00144651) and in a subchronic inhalation study in the rat (MRID No.: 00154784).

C. Occupational / Residential Exposure - Dermal

1. Dermal Absorption

Type of Study: Dermal Absorption Study in the Rat: 870.7600 (§85-2)

MRID No.: 41686201

Executive Summary: In this dermal absorption study, ^{14}C-labeled EPTC (EPTAM 7E) was applied to an area of 29 cm^2 on the backs of male rats (Crl: CD (SR) BR). Animals (28/dose) were dosed at 254, 26.1, 5.68 and 2.73 mg/rat. The application site was covered with a rectangular piece of 1 cm thick foam with a 6 x 7 cm window cut out of the center. The window was placed over the application site, followed by a piece of charcoal impregnated filter. The protective apparatus was held in place with surgical glue and tape. Animals were placed in individual metabolism cages during the exposure; urine and feces were collected at 1 hr, 4 hr, 10 hr, 24 hr.

Total recovery of labeled EPTC ranged from 85 to 100%, with most of the radioactivity (75% to 85%) evaporated from the skin and was absorbed into the charcoal filter. The dose-duration of the exposure did not appear to produce a discernable pattern of absorption. The following table summarized the percent of EPTC absorbed with time at the different dose levels.

Dose (mg/animal)	Percent of Dose Absorbed for Exposure Times			
	1 hr	4 hr	10 hr	24 hr
2.73	**2.13**	**3.85**	**4.58**	**5.59**
5.68	2.41	4.02	3.36	3.08
26.1	2.22	4.29	4.41	5.75
254	1.12	4.73	4.94	8.59

Dermal Absorption Factor: 5% at 10 hour .

Comments about Dermal Absorption: EPTC is a volatile compound and evaporates readily from warm skin. Previous dermal absorption experiments with other thiocarbamates showed that without the charcoal filter over the absorption site, the chemical would either evaporate, resulting in inhalation of the vapors, or condense on the side of the metabolism chamber, resulting on oral exposure. Since both of these unintended routes of exposure could invalidate the dermal absorption study, a system using charcoal impregnated paper was designed to capture the vapors.

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

Type of Study: Acute Neurotoxicity Study in Rats 870.6200 (§81-8)

MRID Nos.: 43039701 and 43297401

Executive Summary: See Acute RfD

Dose and Endpoint for Risk Assessment: LOAEL = 200 mg/kg in males based on neuronal cell necrosis in the brain at the lowest dose tested.

Comments about Study/Endpoint: This dose and endpoint was selected because of the concern for the effects (necrosis in the brain) seen after a single exposure which is appropriate for this exposure period of concern (i.e., 1-7 days). Neuronal necrosis was also observed in male rats following 90 days of oral dosing in the subchronic neurotoxicity study (43230901).

Since a LOAEL was used, a Margin of Exposure (MOE) of 300 is required for occupational exposure. The MOE for residential exposure will be determined during risk characterization by the FQPA Safety Factor Committee. Also, the use of a 5% dermal absorption rate is required for dermal risk assessments, since an oral LOAEL was selected.

This risk assessment is required.

3. Intermediate-Term Dermal (1 Week to Several Months)

Type of Study: Subchronic Neurotoxicity Study in the Rat 870.6200 (§82-7)

MRID No.: 43230901

Executive Summary: In this subchronic neurotoxicity study (43230901), in Alpk:APfSD rats (12/sex/dose, approximately 6 weeks old) were fed diets containing EPTC (98.4%) at 0 (basal diet), 500, 1000, or 2500 ppm (0, 7.9, 39.4, or 193 mg/kg/day, males; 0, 8.8, 43.5, or 205 mg/kg/day, females) for 13 weeks. Clinical observations were made at least once daily, while body weights and food consumption were determined on a weekly basis. Functional Observational Battery (FOB) and motor activity were evaluated at study weeks 1, 5, 9, and 14. At study termination, six animals/sex/dose were perfusion fixed for neurohistopathological evaluation.

One high-dose male was found dead on day 3; the cause of death could not be determined. With the exception of 5/12 high-dose females showing urine incontinence, all other animals survived to terminal sacrifice without the appearance of any treatment-related clinical signs. Mean body weights were statistically significantly ($p \leq 0.05$) lower in mid- and high-dose females and high-dose males, the differences were, however, not biologically significant (5 to 7%). Body weight gains were decreased in mid-dose males (7%, NS) and females (13%, $p \leq 0.05$) and high-dose males (10%, $p \leq 0.05$) and females (17%, $p \leq 0.05$). Food consumption was significantly lower in high-dose males (7.7 to 14%) and females (10.1 to 18.1%). Food utilization did not show any consistent treatment-related effects. At the high-dose, FOB results showed significantly decreased landing foot splay in females and increases in time to tail flick in males. No other consistent treatment-related findings were observed.

At study termination, significant differences were noted in the brain measurements of mid- and high-dose animals. Relative (to body weight) brain weights were significantly decreased in mid- and high-dose females (4.0 and 9.6%, respectively) and high-dose males (2.3%). Relative brain width of high-dose females was decreased (4.1%). For males, no treatment-related differences were noted brain widths and lengths, either absolute or corrected for body weights.

Neuropathological evaluation of the brains revealed treatment-related increases in the incidence of neuronal necrosis (all graded as minimal) in mid- and high-dose males (2/6 and 4/6, respectively), compared to 1/6 control (and low-dose) males. Necrosis was also noted in mid- and high-dose females (1/6 and 5/6, respectively), while no lesions were observed in control and low-dose females.

Based on the results of this study, the NOAEL was 100 ppm (7.9 mg/kg/day, males; 8.8 mg/kg/day, females) and the LOAEL was 500 ppm (39 mg/kg/day, males; 44 mg/kg/day, females) based on decreased body weight gain and relative brain weight in females and neuronal necrosis in the brain in males and females.

Dose and Endpoint for Risk Assessment: NOAEL = 7.9mg/kg in males based on neuronal necrosis at 39 mg/kg/day (LOAEL).

Comments about Study/Endpoint: This study is appropriate for the exposure period of concern (7-days to several months). The endpoint of concern (neuronal necrosis) was also seen in rats following single oral exposure.

The use of a 5% dermal absorption rate is required for dermal risk assessments, since an oral LOAEL was selected.

This risk assessment is required.

4. Long-Term Dermal (Several Months to Lifetime)

Type of Study: None

MRID No. None

Executive Summary: None

Dose and Endpoint for Risk Assessment: Not applicable

Comments about Study and Endpoint: Based on application methods for the uses currently registered, EPTC is typically used as a single annual preplant or preemergence application. Therefore, the potential for long-term worker exposure from the currently registered uses of EPTC is not expected.

This risk assessment is NOT required

5. Inhalation Exposure

Type of Study: 90-Day Inhalation Study in the Rat: 870.3465 (§82-4)

MRID No.: 00154784

Executive Summary: In this subchronic inhalation study, Sprague-Dawley rats (24/sex/dose, 7 to 8 weeks old) were exposed in a whole body chamber to EPTC (98.6%) at concentrations of 0, 8.3, 58 or 290 µg/L 6 hr/day, 5 days/week, for 13 weeks. Interim sacrifices were carried out after 3 weeks and between 9 and 10 weeks on 6 animals /sex/dose/time period and at 14 weeks on 12 animals/sex/dose.

With the exception of one low-dose male, which died of undetermined causes during week 5, all remaining animals survived to terminal sacrifice. Clinical signs were observed at all dose levels, but occurred sooner and with increased incidence in mid-

and high-dose animals. These clinical signs consisted of ocular irritation, chromodacyorrhea, and alopecia; these findings were observed earlier and in greater incidence in mid- and high-dose animals.

Food consumption was significantly lower in mid- and high-dose animals, however, mean body weights were not affected by treatment. Clinical pathology results, showed treatment-related changes in clinical chemistry and clotting time parameters. In high-dose animals, aspartate aminotransferase (AST) activity was significantly increased 1.53-fold in females. At 9 - 10 weeks, brain cholinesterase (ChE) was inhibited in high-dose males (15.0%). and females (13.1%). At study termination, brain ChE activity was decreased in low- mid- and high-dose males (13.4%, 19.7%, and 17.5%, respectively) and mid- and high-dose females (16.0% and 20.0%, respectively). Clotting abnormalities were observed in mid- and high-dose females (increased prothrombin time) and high-dose males (increased partial thromboplastin and stypven times).

Histopathology evaluation revealed increased incidence of myocardial degeneration in high-dose males and females. Although these lesions appear to be treatment-related, control, low-, and mid-dose animals were also affected with no apparent dose-response relationship. Increased severity of the lesions was, however, observed at the high-dose level. Myocardial degeneration was observed as early as 3 weeks at 290 µg/L and consisted of lesions graded as minimum (2/6 males; 6/6 females), slight (3/6 males; 0/6 females), and moderate (1/6 males;0/6 females). Myocardial degeneration was also observed in control animals (minimum, 4/6 males and 4/6 females; slight 1/6 females), however, the grade of the lesion did not appear to as severe as with the high-dose animals.

Since most exposure scenarios for EPTC are within a 3 week time duration, the HIARC selected the NOAEL of 58 µg/L based on the increased incidence and severity of myocardial degeneration observed at 21 days at 290 µg/L (LOAEL).

However, the study NOAEL is 8.3 µg/L and the LOAEL is 58 µg/L based on clinical signs, decreased food consumption, brain ChEI, and increased prothrombin times in females.

Dose and Endpoint for Risk Assessment: See *Comments about Study and Endpoint* below.

Comments about Study and Endpoint: The HIARC selected the 58 µg/L dose as the appropriate NOAEL for short-term (1-7 days) exposure risk assessments since no treatment-related effects were seen during this exposure period of concern.

The HIARC further determined that this NOAEL (58 µg/L) can also be used for conducting risk assessments for exposure scenarios of up to 21 days since the heart lesions were observed at the 3-week interim sacrifice.

However, in the event that exposure scenarios of greater than 21 days are identified, the HIARC recommends the use of the study NOAEL (8.3 µg/L) based on the clinical signs, decreased food consumption, brain ChEI, and increased prothrombin times

observed at 58 µg/L (LOAEL) at study termination. This NOAEL is more appropriate for exposure durations greater than 21 days since the effects were observed after 90 days of exposure.

This risk assessment is required.

D. Margin of Exposure for Occupational/Residential Risk Assessments

A MOE of 300 is required for short-term occupational dermal exposure risk assessments. A MOE of 100 is adequate for intermediate-term occupational dermal exposure risk assessments due to the use of a LOAEL. A MOE of 100 is adequate for occupational short- and intermediate-term inhalation risk assessments. No long-term occupational dermal or inhalation exposure risk assessment is required. The MOEs for residential exposure risk assessments will be determined during risk characterization by the FQPA Safety Factor Committee.

E. Recommendation for Aggregate Exposure Risk Assessments:

For acute aggregate exposure risk assessment, combine the high end exposure values from food + water and compare it to the acute RfD.

For short and intermediate aggregate exposure risk assessments, combine the high end exposure values from food + water with the dermal exposure (converted oral equivalent dose) since the toxicological endpoint is the same (neuronal necrosis).

An aggregate dermal and inhalation risk assessment can not be performed since the toxicological endpoint (clinical signs, alterations in clinical chemistry and hematology parameters, and myocardial degeneration) are different via the inhalation route.

No long-term dermal or inhalation exposure risk assessments are required.

III. CLASSIFICATION OF CARCINOGENIC POTENTIAL

A. Combined Chronic Toxicity/Carcinogenicity Study in Rats

MRID No. 00145004 and 00146311

Executive Summary: In this combined chronic toxicity and oncogenicity study (00145004, 00145311), Charles River CD rats were fed diets containing EPTC to yield final doses of 0 (basal diet), 5, 25, or 125 mg/kg/day (achieved doses: 0, 5.01, 25.0, or 125.8 mg/kg/day in males and 4.97, 24.8, or 124.8 mg/kg/day in females) for either 52 weeks (interim sacrifice, 10 animals/sex/dose) or 104 weeks (50 animals/sex/dose).

Treatment-related clinical signs were observed primarily in high-dose animals. After 85 to 95 weeks of treatment, females, followed shortly thereafter in males, exhibited hindquarter weakness (inability to assume an upright stance). Discolored urine was also observed in high-dose males. Of the main study, high-dose males, only 15/50 survived to terminal sacrifice; males in the low- and mid-dose groups and all female test groups had survival rates

comparable to control values. Ophthalmological examinations revealed an increased incidence of cataracts in high-dose males (13/23 vs. 2/28 for controls).Dose-related decreases in mean body weights were observed in both males and females. For the low-, mid- and high-dose groups, body weights (compared to concurrent control values) were decreased by 7, 15 and 36%, respectively, in males and 10, 16, and 40%, respectively, in females. Parallel decreases were also noted in mean feed consumption.

Clinical pathological evaluation revealed changes in some clinical chemistry and hematology parameters. High-dose males showed clotting abnormalities (increased activated partial thromboplastin and prothrombin times) at all of the evaluation times. BUN and aspartate aminotransferase (AST) were increased in high-dose males and females. Erythrocyte cholinesterase activities were significantly decreased in high-dose males and females; no treatment related changes in brain or plasma cholinesterase activities were seen.

Histopathological examination revealed treatment-related neuromuscular and myocardial lesions in males and females. For mid- and high-dose animals, atrophy and degeneration of muscle adjacent to sciatic nerve in males (31/47 and 37/39, respectively, vs. 1/46 for control) and females (13/50 and 34/43, respectively, vs. 0/47 for control); similar effects were noted in the biceps muscle of mid- and high-dose males and females. Atrophy and degeneration was observed in the sciatic nerves of mid- and high-dose males (37/46 and 33/38, respectively, vs. 10/44 for control and females (31/38 and 38/43, respectively, vs. 7/46 for control). Similar effected were noted in the tibial nerve of mid- and high-dose males and females. Axonal degeneration was noted in the lumbar spinal cords of mid- and high-dose males (40/47 and 25/38, respectively, vs. 21/47 for control) and females (38/50 and 35/48, respectively, vs. 8/47 for control). A lower incidence of axonal degeneration was noted in the sacral spinal cords of mid- and high-dose males (5/41 and 7/38, respectively, vs. 0/46 for control) and females (3/47 and 9/40, respectively, vs. 0/39 for control). The incidence of axonal degeneration in the thoracic spinal cords of treated animals were similar to control values. Increased incidences of myocardial lesions (principally chronic myocarditis, atrophy and/or thrombosis) were observed in mid- and high-dose males (26/60 and 38/60, respectively, vs. 24/60 for control) and high-dose females (39/60 vs. 8/60 for control).

There was no evidence of carcinogenicity. For chronic toxicity, the NOAEL was 5 mg/kg/day and the LOAEL was 25 mg/kg/day based on decreased body weight and increased incidences of myocardial and neuromuscular lesions.

2. Carcinogenicity Study in Mice

MRID No.: 00161596

Executive Summary: In this study, CRL:CD-1(IRC)BR mice (60/sex/dose) were fed diets containing EPTC (98.5%) at concentrations of 0, 200, 600 or 1800 ppm (approximately 0, 30, 90, or 270 mg/kg/day in males and females) for 78 weeks. An interim sacrifice at week 52 was performed on an additional 5 animals/sex/dose.

High-dose showed consistent, significant ($p \leq 0.05$) decreases in body weights of 3 to 13% in males and 10 to 13% in females. Mid-dose females showed a slight (3 to 6%), but statistically significant ($p \leq 0.05$) decreases in body weights at most measurement intervals up to week 68;

body weights of mid-dose males were comparable to control values. Food consumption was significantly ($p \leq 0.05$) deceased by 13.6 to 42% in high-dose females up to week 20; at later time points, sporadic decreases were observed.

The tumor profiles of treated animals were comparable to control values. Malignant neoplasms, benign tumors, and other histopathological lesions generally occurred to the same extent in the control and dose animals. Some types of tumors were more prevalent in on sex (e.g., lymphomas in females and hepatocellular carcinomas/adenomas in males), but were comparable between dietary groups. The doses used in this study were adequate to assess the oncogenic potential of EPTC.

Biologically and toxicologically significant effects were observed at the highest dose tested (270 mg/kg/day), which was adequate to assess the carcinogenic potential of EPTC.

There was no evidence of carcinogenicity in male or female mice. For systemic toxicity, the NOAEL was 90 mg/kg/day and the LOAEL was 270 mg/kg/day based on decreased body weight and food consumption.

3. Classification of Carcinogenic Potential

EPTC has not been formally evaluated for a cancer classification. However, since both the rat and mouse studies were negative with respect to carcinogenesis, the HIARC did not recommend evaluation by the Cancer Peer Review Committee.

V. MUTAGENICITY

A. Reverse Mutation in *Salmonella typhimurium* and *Escherichia coli*:

In this study (MRID No.: 00152451), EPTC (97.2%) was evaluated for mutagenic potential in the rec-assay using strains (HA17 and M45) of *Bacillus subtilis* without metabolic (S9) activation and reverse mutation test (Ames assay), with and without S9 activation using *Salmonella typhimurim* (TA1535, TA1537, TA1538, TA98 and TA100) and *Escherichia coli* (WP2 *hcr* (uvrA)). In both assays, EPTC was tested to the limit of cytotoxicity or solubility. In the rec-assay, mitomycin C was used as the positive control and kanamycin as the negative control. In the Ames assay beta-propiolactone, 2-aminoanthracene, 9-aminoacridine and 2-nitroflourene were used as positive controls. In both assays DMSO solvent controls were used. EPTC did not induce DNA damage in *B. subtilis rec*$^-$ M45 strain at concentrations from 1 to 100% (v/v) without S9 activation. Further, EPTC did not induce a mutagenic response in the Ames assay with or without S9 activation at doses from 10 to 5000 µg/plate. Positive control materials for all tester strains induced large numbers of revertants over the solvent control, confirming the sensitivity of the assay.

B. Forward Gene Mutation in Mouse Lymphoma Cells:

In this study (00152454), EPTC (98.6%) was evaluated for mutagenic potential in L5178Y (TK+/-) mouse lymphoma cells with and without metabolic (S9) activation. EPTC, over a dose range of 0.006 to 3.0 µg/mL, showed dose-related cytotoxicity at dose levels greater than or equal to 0.023 µg/mL with and without S9 activation. In the mutagenicity assay,

EPTC was evaluated over a dose range of 0.0125 to 0.1500 µg/mL without S9 activation and, 0.005 to 0.06 µg/mL with S9 activation. Under conditions of this assay, EPTC induced a slight mutagenic effect at dose levels of 0.05 and 0.06 µg/mL in the presence of S9 activation and over a dose range of 0.0125 to 0.15 µg/mL in the nonactivated system.

C. Chromosome Aberration in Mouse Lymphoma Cells:

In this study (MRID No.: 00152455) the mutagenic potential of EPTC (98.6%) was evaluated in a chromosomal aberration assay in mouse lymphoma cells. EPTC concentrations ranged from 0.0125 to 0.15 µg/mL without metabolic (S9) activation and 0.005 to 0.06 µg/mL with S9 activation. Solvent (DMSO) and positive controls (N-nitrosodimethylamine) were also evaluated. EPTC was cytotoxic above concentrations of 0.023 µg/mL or higher with and without S9 activation. EPTC did not induce a dose-related statistically significant increase in chromosomal aberrations compared to the concurrent solvent control. Therefore, EPTC was not considered mutagenic/clastogenic in mouse lymphoma cells L5178Y over dose ranges of 0.0125 to 0.15 µg/mL without S9 activation or o.005 to 0.06 µg/mL with S9 activation.

D. Chromosome Aberrations in vitro (CHO cells)

In this study (00161601), EPTC (% purity not stated) was evaluated for inducing chromosome aberrations in CHO cells treated at a doses of 30, 60, 90, 120, 150 or 200 µg/mL without metabolic activation (S9) and 15, 30 75, 150, 225 or 300 µg/mL with S9 activation. In the absence of S9 activation, no dividing cells were observed at EPTC doses of 150 and 200 µg/mL and 20% reduction (non-significant) in monolayer confluency, combined with observable deceases in mitosis, at 90 and 120 µg/mL. At doses of 30 to 60 µg/mL no significant increases in chromosomally aberrant cells over controls were found. The positive control, MMC, induced large increases in aberrant cells (26%), the number of aberrations per cell (> 0.32 vs. 0.03 for controls), and multiple aberrant cells (4.0% vs. 0.5%).

In the presence of S9 activation, EPTC at 225 and 300 µg/mL were lethal. At 150 µg/mL there was moderate reduction in confluency (25%), and slightly reduced number of observable mitotic cells. There was no significant increase in chromosome aberrations at 15, 30, 75 or 150 µg/mL (2.5%, 1.0%, 1% and 4%, respectively). Positive controls treated with CP resulted in 36% of the cells with aberrations overall,, at a rate of 0.48 aberrations per cell, and 8.0% with more than one aberration.

From the results of this assay, EPTC was negative for the induction of chromosome aberrations in CHO cells with or without S9 activation.

E. Chromosome Aberrations *in vitro* (rat hepatocytes):

In this study (00161600), EPTC (98.5%) was evaluated in a primary DNA damage/repair assay in isolated primary rat hepatocytes. The hepatocytes were exposed to graded concentrations of EPTC (0.1 to 5000 µg/mL, preliminary assay; 3 to 500 µg/mL, replicate assay) together with 10 µCi/mL ^{3}H- thymidine for 19 to 21 hr incubation at 37°C. The cells were washed, swelled in hypotonic saline, fixed, and prepared for autoradiographic grain counts. 2-AAF was used as a positive control.

EPTC was cytotoxic at concentrations of 250 µg/mL and above; precipitation was noted at 1000 and 5000 µg/mL. In contrast to the positive UDS response in the majority of ce3lls treated with 2-AAF (39.5 NG in 95% of cells in the first experiment and 5.7 NG in 52% in the second assay), test plates were negative at all useful concentrations of EPTC up to the nontoxic level of 100 µg/mL, registering negative NG values in the few cells with any grains (not different from the negative controls).

F. Mutagenic Potential in *Drosophia:*

In this published article (00153248), the mutagenic potential of 99% EPTC (one of 53 compounds tested) and evaluated in *Drosophila.* EPTC was administered for 3 days to Canton-S males either in the diet at 150 ppm or intra abdominally at 1250 ppm. The doses were selected to produce 30% mortality. Individual flies were mated 3, 5, and 7 days after dosing to mutant (*Basc*) females.

Based on the results of the study, EPTC was negative for inducing sex-linked recessive lethals (SLRC). The frequency of lethals in the progeny from EPTC-fed males was 7/5531 (0.13%) and from injected flies, 7/5048 (0.14%).

G. Summary of Mutagenicity Findings

EPTC has intrinsic genotoxicity which is not expressed in either the micronucleus test or the Drosophila SLRC. This is supported by lack of a carcinogenic effect in long-term studies and no genetic component in reproduction and developmental studies. The 1991 guidelines have been satisfied.

VI. FQPA CONSIDERATIONS

1. Adequacy of the Data Base

The toxicology database for EPTC were found to be adequate to for evaluation of FQPA. The following studies were reviewed:

Acute delayed neurotoxicity studies in hen (MRID Nos.: 00141374 and 00150325).

Acute (MRID No.: 43297401) and subchronic (MRID No.: 43232901) neurotoxicity studies in the rat

Developmental toxicity studies in rat (MRID No.: 00138919) and rabbit (MRID No.: 40442302)

Two-generation reproduction studies in the rat (MRID Nos.:0012128, 440420408, and 00161597).

2. Neurotoxicity Data

In this acute delayed neurotoxicity study (MRID No.: 00150325), hens (10/dose) were dosed with EPTC (98.4%) at 4674 mg/kg (LD_{50}) and observed for 21 days. Surviving hens were redosed with EPTC and observed for an additional 21 days. Negative (corn oil) and positive (TOCP, 500 mg/kg) control groups were included in the study. At termination of the study, no histopathological evidence of neurotoxicity was observed in the EPTC-treated hens. All TOCP-treated hens, however, had significant neurological degeneration in one or more spinal cord levels, as well as peripheral nerves.

In another acute delayed neurotoxicity study (MRID 00141374), hens (12/dose) were gavaged with EPTC (98.6%) at 7200 mg/kg (LD50 = 7171 mg/kg) and observed for 21 days. Surviving hens were redosed on day 22 with EPTC and observed for an additional 21 days. Negative (corn oil) and positive (TOCP, 500 mg/kg) control groups, each with 12 hens, were included in the study. At termination of the study, hens were sacrificed and examined for neurohistopathological lesions At termination of the study, no histopathological evidence of neurotoxicity was observed in the EPTC-treated hens. All TOCP-treated hens, however, had significant neurological degeneration in one or more spinal cord levels, as well as peripheral nerves.

In an acute neurotoxicity study in Alpk:APfSD rats (discussed in detail in Section II. Acute RfD), the in males a NOAEL was not established; the LOAEL was 200 mg/kg based on neuronal cell necrosis in the brain. In females, the NOAEL was 200 mg/kg and the LOAEL was 1000 mg/kg based on clinical signs, death, and neuronal cell necrosis in the brain (MRID Nos. 43039701 and 43297401).

In a subchronic neurotoxicity study (discussed in detail in Section II.C. Intermediate-Term Dermal), the NOAEL was 7.9 mg/kg/day in males and 8.8 mg/kg/day in females and the LOAEL was 30 mg/kg/day in males and 44 mg/kg/day in females based on decreased body weight gain and relative brain weight in females and neuronal necrosis in the brain in males and females (MRID No.: 43230901).

In a combined chronic toxicity/carcinogenicity study in rats (MRID Nos.: 00145004 and 00145311), hstopathological examination revealed treatment-related neuromuscular and myocardial lesions in males and females. For mid- and high-dose animals, atrophy and degeneration of muscle adjacent to sciatic nerve in males (31/47 and 37/39, respectively, vs. 1/46 for control) and females (13/50 and 34/43, respectively, vs. 0/47 for control); similar effects were noted in the biceps muscle of mid- and high-dose males and females. Atrophy and degeneration was observed in the sciatic nerves of mid- and high-dose males (37/46 and 33/38, respectively, vs. 10/44 for control and females (31/38 and 38/43, respectively, vs. 7/46 for control). Similar effected were noted in the tibial nerve of mid- and high-dose males and females. Axonal degeneration was noted in the lumbar spinal cords of mid- and high-dose males (40/47 and 25/38, respectively, vs. 21/47 for control) and females (38/50 and 35/48, respectively, vs. 8/47 for control). a lower incidence of axonal degeneration was noted in the sacral spinal cords of mid- and high-dose males (5/41 and 7/38, respectively, vs. 0/46 for control) and females (3/47 and 9/40, respectively, vs. 0/39 for control). The incidence of

axonal degeneration in the thoracic spinal cords of treated animals were similar to control values. Increased incidences of myocardial lesions (principally chronic myocarditis, atrophy and/or thrombosis) were observed in mid- and high-dose males (26/60 and 38/60, respectively, vs. 24/60 for control) and high-dose females (39/60 vs. 8/60 for control).

In the chronic toxicity study in Beagle dogs histopathological evaluation of high-dose males and females, revealed Wallerian-type degeneration (described as swelling and/or degeneration of axons and/or myelin sheaths, plus the presence of lipid-laden macrophages and/or proliferating Schwann cells) in the spinal cords and various peripheral nerves (sciatic, sacral, and tibial nerves). One male which was sacrificed during the study showed widespread and very severe degenerative lesions in peripheral nerves as well as at all levels of the spinal cord, extending into the brain stem as well as the brain itself (cerebellar peduncles). Degenerative changes in the skeletal and cardiac muscle were also observed.

3. Developmental Toxicity

In an acceptable (guideline) developmental toxicity study), female COBS CD rats (25/dose) were gavaged with EPTC (assumed 100%) at doses of 0 (vehicle, corn oil), 30, 100, or 300 mg/kg/day on gestation days (GD) 6 through 15. Treatment-related clinical observations were limited to high-dose animals. Starting on gestation day 7, all high-dose animals showed signs of wet, matted, stained urogenital region and red matter in the facial area and/or various other body surfaces. Between GD 11 and 17; 13 deaths occurred. High incidences of "metrorrhagia", severe internal hemorrhage, or cardiorespiratory arrest were observed at necropsy evaluation of these animals. Systemic maternal toxicity consisted of significant decreases in mean body weight (12 to 17%), body weight gain (-17 g to 64 g, vs. 34 g and 103 g, respectively for controls) and adjusted mean body weight change (13.6 g vs. 33.8 for control). Mean food consumption of high-dose animals (as % of control) was markedly decreased during GD 6 to 9 (43%), GD 9 to 12 (23%), and GD 12 to 16 (43%). The high incidence of maternal mortality in the high-dose group resulted in 6 litters with viable fetuses surviving to scheduled sacrifice compared with 22, 19, and 21 litters in the control, low- and mid-dose groups, respectively. Post-implantation loss/litter for control, low-, mid-, and high-dose females was 0.5, 0.6, 1.2, and 2.1, respectively. The high number of losses in the mid- and high-dose groups was attributed a reduction in the number of viable fetuses in the mid- and high-dose groups due to complete (early) litter resorption in one high-dose female and one mid-dose female with total (early) litter resorptions and one with several early resorptions. Reproductive data available from post-mortem examination of high-dose animals which died on study showed early and late resorptions to be 3.4 and 1.2/dam, respectively, the number of corpora lutea to be 11.1/dam, and the number of normal implants to be 7.3/dam. Mean fetal body weight was significantly reduced (2.8 g vs 3.4 g for control) in high-dose litters. In control, low-, mid- and high dose groups, the percent of malformed fetuses was 0.0, 0.4 (omphalocele), 0.4 (absent arteriosus and abnormal great vessels), and 2.6 omphalocele), respectively and the percent of litters with malformed fetuses was 0.0, 5.3, 4.8, and 33.3 ($p \leq 0.05$). Historical control values for the percent of litters and percent of fetuses with omphalocele were 0.0 to 4.5% and 0.0 to 0.3%, respectively. a significant number of high-dose litters had fetuses with unossified sternebrae Nos. 1, 2, 3, and/or 4.

For maternal toxicity, the NOAEL was 100 mg/kg/day and the LOAEL was 300 mg/kg/day and was based on lethality, decreased body weight, body weight gain, corrected body weight gain, and food consumption.

For developmental toxicity, the NOAEL was 100 mg/kg/day and the LOAEL was 300 mg/kg/day based on decreased fetal body weight, decreased litter size, increased resorptions, increased incidence of omphalocle and increased incidence of unossified sternebrae (MRID No.: 00138919).

In an acceptable (guideline) developmental toxicity study , pregnant New Zealand White rabbits (16/dose, except at the high-dose which had 18 animals) were dosed with EPTC at 0 (vehicle, corn oil control), 5, 40, or 300 mg/kg/day from gestation day (GD) 7 through 19. Treatment-related clinical findings were limited to high-dose animals and consisted of loose stools (9/18), hematuria (4/18), salivation (1/18), stained nose or lip (2/18), wet fur coat (3/18). Two high-dose does died on GD 20, these animals also showed decreased body weights and decreased food consumption prior to death; one control doe also died on GD 23. Systemic maternal toxicity (decreased body weight and food consumption) were limited to high-dose does. Serum and erythrocyte ChE activities were all statistically significantly ($p \leq 0.05$) decreased in treated does. Serum ChE activity was inhibited by 9.9%, 17.6% and 56% in the low-, mid-, and high-dose groups, respectively, and erythrocyte ChE, by 12.6% and 68% in the mid-dose and high-dose groups, respectively.

At termination of the study, necropsy findings of treated animals were comparable to control values. Further, no differences in mean and absolute organ weights between control and treated animals was observed. Changes in intrauterine finding were observed were generally limited to high-dose does and consisted of a reduction in the mean fetal body weight (35.3 g vs. 40.3 g for control, $p \leq 0.05$) and an increase in the percent of malformed fetuses (7.4% vs. 2.4% for control) and affected implants (13.1% vs. 5.0% for control). Although the percent of post-implantation losses in the mid- and high-dose does (7.2 and 6.2%, respectively) was greater than that of the controls (2.8%, none of the values were significantly different from the concurrent control values and none were outside of the historical control ranges of 2 to 19% for percent postimplantation loss, 1.4 to 18.1% for percent of malformed fetuses, and 4.6 to 25.4% for percent of affected fetuses.

Despite the findings for individual litters, no overall statistically significant increases over control were recorded for external, visceral, and skeletal anomalies were observed in any of the treatment groups. Convoluted retinas without hemorrhage were reported in four fetuses of two litters at the low-dose, one fetus at the mid-dose, three fetuses from three litters at the high-dose. For the high-dose group, gallbladders were absent in two fetuses from two litters, while reduced gallbladder was observed in all treatment groups. Both the convoluted retina and reduce gallbladder appear to be common findings in the performing laboratory.

Litters of three of the adversely affected does in the high-dose had two fetuses with extremely convoluted retinas, blood-filled eye sockets and/or vitreous bodies; one fetus with forefoot overflexion and cleft palate; and one with malformed centra of the thoracic vertebrae. The fetal effects were considered to be secondary to the marked maternal toxicity at the high-dose.

For maternal cholinesterase inhibition., the LOAEL was 5 mg/kg/day based on inhibition of serum ChE (9.9% inhibition); a NOAEL was not established.

For maternal systemic toxicity, the NOAEL was 40 mg/kg/day and the LOAEL was 300 mg/kg/day based on mortality, clinical signs and decreased body weight and food consumption (MRID No.: 40442302).

Based on the results of this study, the LOAEL for developmental toxicity was not established, the NOAEL was ≥ 300 mg/kg/day (HDT).

4. Reproductive Toxicity Study

In an acceptable (guideline) two-generation, two litter reproduction study, EPTC (98.4%) was administered to weanling (no age given) Crl:CD(SD)Br rats (30/sex/dose) at dietary levels of 0, 50, 200, or 800 ppm (calculated doses: 0, 3.75, 15, or 60 mg/kg/day).
There were no treatment-related clinical findings or deaths. At the high-dose level, body weights during the pre-mating period were statistically significantly ($p \leq 0.05$) decreased in F_0 males (6.5 to 12.1%, weeks 8 to 23) and females (9.2 to 8.5%, weeks 8 to 12), and in F_1 males (13 to 19.5%, weeks 0 to 23) and females (7.3 to 12.2%, weeks 0 to 12). Body weights were significantly decreased by 6.3 to 9.1% in F_0 females and 10.8 to 12.8% in F_1 females from GD 0 to 20. During lactation, body weights of F_0 females were decreased by 10.9% only on day 0, while that of F_1 females was decreased by 8.8 to 14.2% throughout the lactation period. Food consumption was significantly reduced during pretreatment high-dose F_0 males and low-, mid- and high dose F_1 males. Food consumption was reduced in high-dose F_1 females with sporadic decreased noted at the low- and mid-dose levels. During the first week of gestation, food consumption was decreased only in high-dose F_1 females.

Evaluation of clinical pathology parameters did not reveal any treatment-related changes; brain, plasma, and erythrocyte ChE activities of treated animals were comparable to control values.

Post-mortem observations and gross necropsy findings of adult animals did not suggest any parental toxicity. Histological findings of F_0 tissues revealed only incidental findings. However, after weaning of the F_{2a} litters, the incidence of degenerative cardiomyopathy in F_1 adults was 4/25, 3/25, 15/25 and 25/25 in control, low-, mid- and high-dose males, respectively, and 1/25, 0/25, 5/25 and 25/25 control, low-, mid- and high-dose females, respectively; hearts were not examined in the F_0 animals.

Mean body weights of F_{1a} and F_{1b} high-dose pups were statistically significantly ($p \leq 0.05$) in males (9.2 to 21%, weeks 0 to 21) and females (16 to 25%, weeks 4 to 21). No other treatment-related differences were noted in any of the other reproductive parameters.

For parental systemic toxicity, the NOAEL was 2.5 mg/kg/day and the .LOAEL was 10 mg/kg/day based on degenerative cardiomyopathy.

For developmental toxicity, the NOAEL was 10 mg/kg/day and the LOAEL was 40 mg/kg/day based on decreased mean pup weight during lactation days 4 to 21.

For reproductive toxicity, the NOAEL was 40 mg/kg/day (HDT); a LOAEL was not attained).

In another two-generation, two-litter reproduction study, 6 to 8 week old weanling Sprague-Dawley Crl CD (SD) BR rats (15/dose, males; 30/dose, females) were administered EPTC (98.6%) at dietary levels of 0, 40, 200, or 1000 ppm (calculated doses: 0, 2, 10, or 50 mg/kg/day). Exposure of the test material to all animals was continuous in the diet throughout the study (MRID No.: 0012128, 440420408).

No adverse, treatment-related clinical findings were observed during the study. Mean body weights were statistically significantly ($p \leq 0.05$) decreased in high-dose F_0 females (10%) and F_1 males (16%) and females (13%); the body weights of F_0 males were not affected by treatment. For F_0 females (F_{1b} litter) mean body weights were decreased by about 9% during gestation and 10% to 14% during lactation. For F_1 females (F_{2b} litter) mean body weights were decreased by about 9% during gestation and 11 to 14% during lactation. Terminal body weights were significantly decreased in F_0 females (10%) and F_1 males (18%) and females (15%). Along with the observed decreases in body weights, there were also parallel decreases in food consumption.

No treatment-related effects were noted for any of the reproductive parameters in either male or female parents for either mating or generation. Pup survival indices of treatment groups were comparable to that of the controls. Mean body weights of F_{1a}, F_{1b} and F_{2a} high-dose pups were statistically significantly decreased lactation days 14 and 21. Mean body weights were significantly decreased for F_{1a} (male, 15% and female, 18%) and F_{1b} (male, 15% and female 18%) weanlings. No treatment-related changes were noted in any of the developmental landmarks.

Although differences in absolute and relative organ weights were observed in high-dose animals, in most cases, the changes did not appear to be treatment-related and may be a reflection of decreased body weights; further, there was no supporting histopathological evidence.

Necropsy findings of adult animals revealed treatment-related toxicity. Histological evaluation of the hearts revealed a highly significant ($p \leq 0.1$) increase in the incidence of myocardial degeneration; the severity grade of the lesion (minimal to slight) increased with increasing dose. For F_0 females in the control, low-, mid- and high-dose groups, the incidence of degeneration was 6/30, 7/30, 11/30 and 26/30, respectively. For control, low-, mid- and high-dose F_1 animals, the incidences were 5/15, 11/15, 8/15, and 15/15, respectively, in males and 8/30, 8/30, 5/30, and 25/30, respectively, in females. For F_0 males, the incidences of 12/15, 13/15, and 13/15 were noted in the low- mid-, and high-dose groups, none of which were significantly different from the control value of 8/15. The cardiac lesion was characterized by the study authors as multifocal hyaline or smooth deeply eosinophilic staining (H&E) myocardial muscle bundles often accompanied by loss of normal structure, proliferation of sacrolemmal cells and/or infiltration by histocytes and mononuclear inflammatory cells. Other histological effects included degeneration, with calcification, of the

kidney epithelial tubules. This effect was observed in high-dose (low- and mid-dose kidneys were not evaluated) F_0 males (5/15 *vs* none in control, $p \leq 0.01$) and control, low-, mid-, and high-dose females (11/30, 19/30, 18/30 and 22/30, $p \leq 0.01$).

For parental systemic toxicity, the LOAEL was 2 mg/kg/day based on degenerative cardiomyopathy in males and renal tubule degeneration in females; a NOAEL was not established.

For reproductive toxicity, the NOAEL was 50 mg/kg/day and the LOAEL was >50 mg/kg/day.

For developmental toxicity, the NOAEL was 10 mg/kg/day and the LOAEL was 50 mg/kg/day based on decreased pup weight during postnatal day 14 to 21.

5. Determination of Susceptibility

The data provided no indication of increased susceptibility of rats or rabbits *in utero* and/or post natal exposure to EPTC. In the prenatal developmental toxicity study in rats, developmental toxicity was seen in the presence of maternal toxicity. In the developmental toxicity study in rabbits, no evidence of developmental toxicity was seen even in the presence of maternal toxicity at the highest dose tested. In the two-generation reproduction study in rats, effects in the offspring were observed only at or above treatment levels which resulted in evidence of parental toxicity.

6. Determination of the Need for Developmental Neurotoxicity Study:

The HIARC determined that a developmental neurotoxicity study in rats was required based on the following:

(I). Evidence supporting a developmental neurotoxicity study:

- Acute, subchronic, and chronic exposure to EPTC produced neuronal cell necrosis in the central and/or peripheral nervous systems of rats and dogs.
- Acute exposure to other thiocarbamates (cycloate, pebulate, and vernolate) produced neuronal cell necrosis similar to that of EPTC (MRID No. 43948301).

(ii). Evidence that does not support a developmental neurotoxicity study:

- No *in utero* developmental and reproductive toxicity were observed in the absence of maternal effects.
- No acute delayed neurotoxicity was observed in hens.

7. Determination of the FQPA Factor

Based solely on the hazard assessment, the HIARC recommends to the FQPA Safety Factor Committee that the additional factor for the protection of infants and children from exposure to EPTC (as required by FQPA) be retained. The final determination will, however, be made during risk characterization by the FQPA Safety Factor Committee.

VII. HAZARD CHARACTERIZATION

The database for EPTC is adequate to assess the toxicology hazard profile. Toxicological effects of concern include cardiomyopathy and neuronal cell necrosis. Both of these findings were observed in several studies of varying length of time and in different species.

Cardiotoxicity was observed in subchronic and long-term studies, and, in general, the severity and incidence of the lesion increased with increasing dose of EPTC. In 90-day feeding and inhalation studies and in two chronic feeding/oncogenicity studies, all in the rat, histopathological evaluation revealed myocardial degeneration. Additional studies in the rat, revealed cardiac degeneration in adult animals in two separate two-generation reproduction studies. In two chronic studies in the dog, degenerative changes in the cardiac muscle were observed when EPTC was administered in a capsule, but not when administered (at comparable doses) in the diet. In both of the dog studies, electrocardiograms were taken, but only one high-dose male in the capsule study had changes which were described as "potentially" treatment-related.

Other findings of toxicological concern are the increased incidence and severity of neuronal necrosis/degeneration in both the central and peripheral nervous systems of both rats and dogs. In the neurotoxicity studies in the rat, dose-related increases in the incidence of neuronal necrosis was observed in the brains after acute and subchronic exposure to EPTC. Similar neuronal lesions were observed with other thiocarbamates. In both of the combined chronic toxicity/oncogenicity studies in the rat and in the chronic (capsule) study in the dog, treatment-related neuromuscular lesions were observed. In all of these studies hindquarter weakness was observed, and at necropsy evaluation, atrophy and degeneration of the skeletal muscle was observed. In the dog study, the lesion was described a Wallerian-type degeneration in the spinal cords and various peripheral nerves.

There do not appear to be any concern about the reproductive or developmental toxicity of EPTC. In the prenatal developmental toxicity study in rats, developmental toxicity was seen in the presence of maternal toxicity. In the developmental toxicity study in rabbits, no evidence of developmental toxicity was seen even in the presence of maternal toxicity at the highest dose tested. In the two-generation reproduction study in rats, effects in the offspring were observed only at or above treatment levels which resulted in evidence of parental toxicity.

EPTC is also not carcinogenic. In oncogenicity studies in both the rat and mouse, there was no indication that exposure to EPTC resulted in an increased incidence of neoplastic lesions. EPTC has intrinsic genotoxicity which is not expressed in either the micronucleus test or the Drosophila SLRC. This is supported by lack of a carcinogenic effect in long-term studies and no genetic component in reproduction and developmental studies.

VIII. DATA GAPS

In addition to the need for a developmental neurotoxicity study in the rat (§83-6), the HIARC recommended that a 21-day dermal toxicity study (§82-2) with technical EPTC and a metabolism study (§85-1) be performed.

IX. ACUTE TOXICITY ENDPOINTS:

Acute Toxicity of EPTC

Guideline No.	Study Type	MRID No.	Results	Toxicity Category
81-1	Acute Oral	157868	LD50: 1465 mg/kg (M) 1712 mg/kg (F)	III
81-2	Acute Dermal	157869	LD50: > 2000 mg/kg (M) > 2000 mg/kg (F)	III
81-3	Acute Inhalation	157870	LC50: 1.39 mg/L (combined)	II
81-4	Primary Eye Irritation	157871	PIS (24 hr) = 2.2 Reversed within 3 days	III
81-5	Primary Skin Irritation	157872	PII = 1.4	IV
81-6	Dermal Sensitization	157873	Very slight sensitizer	N/A
		41709201	Weak sensitizer (Magnusson-Kligman)	

X. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

The doses and toxicological endpoints selected for various exposure scenarios are summarized below.

EXPOSURE SCENARIO	DOSE (mg/kg/day)	ENDPOINT	STUDY
Acute Dietary	LOAEL=200 (LDT)	Neuronal necrosis in the brain	Acute Neurotoxicity in the Rat
	UF=300 (10x,10x, 3x for LOAEL)	**Acute RfD = 0.67 mg/kg**	
Chronic Dietary	NOAEL=2.5	Parental toxicity, dose-related increase in degenerative cardiomyopathy	Two-Generation Reproduction Study the Rat
	UF=100 (10X10)	**Chronic RfD = 0.025 mg/kg/day**	
Short-Term[a] (Dermal)	Oral LOAEL=200	Neuronal necrosis in the brain.	Acute Neurotoxicity in the Rat
Intermediate-term (Dermal)[a]	Oral NOAEL = 9	Decreased body weight and relative brain weight and neuronal necrosis	90-Day Neurotoxicity Study in the Ra
Long-Term (Dermal)	The use pattern does not indicate the need for long-term dermal risk assessment.		
Inhalation (Short-Term)	NOAEL = 58 µg/L	Myocardial degeneration observed at 21 days in a 90-day inhalation study	90-day Inhalation Study in the Rat
Inhalation (Intermediate-Term, Less than 21 Days)	NOAEL = 58 µg/L	Myocardial degeneration observed at 21 days in a 90-day inhalation study	90-day Inhalation Study in the Rat
Inhalation (Intermediate-Term, Greater Than 21 Days))	NOAEL = 8.3 µg/L	Clinical signs, decreased food consumption, brain ChEI in males, and increased prothrombin times in females.	90-day Inhalation Study in the Rat
Long-Term (Dermal)	The use pattern does not indicate the need for long-term inhalation risk assessment.		

a = The use of a 5% dermal absorption rate is required for dermal risk assessments.