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**DATE:** **December 1, 1998**

**MEMORANDUM**

**SUBJECT:** **EPTC** - Updating Executive Summaries

**FROM:** Robert F. Fricke
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Robert F. Fricke 1 Dec 98

**TO:** Alan Nielsen, Branch Senior Scientist
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The Executive Summaries for the following DERs have been updated to comply with the current format. The upgraded Executive Summaries should be used to upgrade the Toxicology One-Liner Database.

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| 1 | 81-7(a) Acute Delayed Neurotoxicity - Hen | MRID No.: 00150325<br>HED Doc No.: 005190 |
| 2 | 81-7(a) Acute Delayed Neurotoxicity - Hen | MRID No.: 00141374<br>HED Doc No.: 004259 |
| 3 | 81-7(b) Acute Neurotoxicity - Rat | MRID Nos: 43039701, 43297401, 43948301, 43964301<br>HED Doc No: 010837, |
| 4 | 82-1(a) 90-Day Oral Toxicity - Rat | MRID No.: 00144651<br>HED Doc No.: 005156 |
| 5 | 82-1(b) 90-Day Oral Toxicity - Dog | MRID No.: 00150327<br>HED Doc No.: 005190 |
| 6 | 82-4 90-Day Inhalation Toxicity - Rat | MRID No.: 00154784<br>HED Doc No.: 005130 |

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|---|---|---|
| 7 | 82-5(b) 90-Day Neurotoxicity - Rat | MRID No.: 43232090, 43948301, 43964401<br>HED Doc No.: 011311 |
| 8 | 83-5(a) Chronic Feeding - Oncogenicity - Rat | MRID No.: 00145004<br>HED Doc No.: 005055 |
| 9 | 83-1(b) 1-Year Dog (feeding) | MRID No.: 00161595<br>HED Doc No.: 005740 |
| 10 | 83-1(b) 1-Year Dog (oral capsule) | MRID No.: 40442301<br>HED Doc No.: 006797 |
| 11 | 83-2(b) Carcinogenicity - Mouse | MRID No.: 00161596<br>HED Doc No.: 005740 |
| 12 | 83-3(a) Developmental Toxicity - Rat | MRID No.: 00138919<br>HED Doc No.: 004797 |
| 13 | 83-3(b) Developmental Toxicity - Rabbit | MRID No.: 40442302<br>HED Doc No.: 006797 |
| 14 | 83-4 2-Generation Reproduction - Rat | MRID No.: 0012128, 440420408<br>HED Doc No.: 004277, 006797 |
| 15 | 83-4 2-Generation Reproduction - Rat | MRID No.: 00161597<br>HED Doc No.: 005740 |
| 16 | 84-2 Mutagenicity - Ames Assay | MRID No.: 00152451<br>HED Doc No: 004522 |
| 17 | 84-2 Mutagenicity - Mouse Lymphoma Assay | MRID No.: 00152454<br>HED Doc No.: 004522 |
| 18 | 84-2 Mutagenicity - Mouse Micronucleus Assay | MRID No.: 00142895<br>HED Doc No.: 005089 |
| 19 | 84-2 Mutagenicity - Mouse Lymphoma Assay | MRID No.: 00152455<br>HED Doc No.: 004522 |
| 20 | 84-2 Mutagenicity - Carom. Aberration Assay | MRID No.: 00161601<br>HED Doc No.: 005740 |
| 21 | 84-2 Mutagenicity - Sex Link Recessive | MRID No.: 00153248<br>HED Doc No.: 005090 |
| 22 | 84-2 Mutagenicity - DNA Damage/Repair | MRID No.: 00161600<br>HED Doc No.: 005740 |
| 23 | 84-2 Mutagenicity - Mouse Lymphoma Assay | MRID No.: 00161602<br>HED Doc No.: 005740 |
| 24 | 85-2 Dermal Absorption - Rat | MRID No.: 008258<br>HED Doc. No.: 008258 |

**1) Acute Delayed Neurotoxicity Study in the Hen:**

**Citation**: Roberts, N.; Phillips, C.; Gopinath, C. (1984) Acute Delayed Neurotoxicity Study with

EPTC Technical in the Domestic Hen: Report No. PPG 12/84676, Huntingdon Research Centre, MRID No.: 00150325, Unpublished

**Executive Summary**: In this acute delayed neurotoxicity study (MRID 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.

No EPTC-treated hens lost weight, became subdued and/or unsteady. All surviving hens recovered by day 7. At termination of the study, no histopathological evidence of neurotoxicity was observed in the EPTC-treated hens. All TOCP-treated hens, however, exhibited ataxia, which became progressively worse over time. Neuropathological evaluation of the TOCP-treated hens had significant neurological degeneration in one or more spinal cord levels, as well as peripheral nerves.

This study is classified as acceptable (guideline), and satisfies requirements (§81-7a) for an acute delayed neurotoxicity study in the hen.

**2) Acute Delayed Neurotoxicity Study in the Hen**:

**Citation**: Sprague, G. (1981) Acute Delayed Neurotoxicity Study with Technical Eptam in Adult Hens: T-6537, Report No.: T-6537, Stauffer Chemical Co, MRID No.: 00141374, Unpublished

Executive Summary: In this acute delayed neurotoxicity study (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 were ataxic, and had significant neurological degeneration in one or more spinal cord levels, as well as peripheral nerves.

**This study is classified as ACCEPTABLE - GUIDELINE, and satisfies requirements (§81-7a) for an acute delayed neurotoxicity study in the hen.**

**3) Acute Neurotoxicity Study in the Rat**

**Citations**: Bammer, A., Acute Neurotoxicity Study in Rats, Report No.: CTL/P/4092, Study No.: AR5527, Zeneca Central Toxicology Laboratory, UK, October 18, 1993, MRID No.: 43039701, Unpublished.

Stonard, M. and Berry, D., Response to EPA Review and Comments, EPTC: Acute

Neurotoxicity Study in Rats, Addendum 1 to MRID No. 43297401, , Report No.: WRH-070694, Zeneca Central Toxicology Laboratory, UK, July 6, 1994, MRID No.: 43297401, Unpublished.

Chalmers, D.J., Duffel, S.J., and Horner, S.A., Thiocarbamates: Selective Re-examination of Neuropathology, Report No. CTL/P/4618, Study No.: PR0999, Zeneca Central Toxicology Laboratory, UK, March 28, 1995, MRID No.: 43948301, Unpublished.

Bammer, A, First Revision to EPTC: Acute Neurotoxicity Study in Rats, Addendum to 43039701Report No.: CTL/P/4092, Study No.: AR5527, Zeneca Central Toxicology Laboratory, UK, December 1, 1995, MRID No.: 43964301, Unpublished.

**Executive Summary**: In this acute neurotoxicity study (43039701, 43297401, 43948301, ), 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. Clinical observations were made at least once daily, while body weights, Functional Observational Battery (FOB) and motor activity were evaluated at prestudy (day -1), 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 (6 and 16%, 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. Decreased motor activity was observed in males and female at the mid- and/or high-dose levels. For the first five minutes post-dosing, mid- and high-dose males and high-dose females showed significantly lower motor activity; overall motor activity was similar to control values.

Brain measurements at terminal sacrifice revealed statistically significant decreases in weight of mid- and high-dose males (5.5 and 6.5%, respectively) and females (2.7 and 3.3%, respectively) compared to control values. The brain length of high-dose males was reduced by 3%.

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, the LOAEL was established at 200 mg/kg in males (neuronal cell necrosis in the brain) and 1000 mg/kg in females (clinical signs, death, and neuronal cell necrosis in the brain). The NOAEL was not established in males and established at 200 mg/kg in females.

This study is acceptable (guideline), and satisfies requirements (§81-7b) for an acute neurotoxicity study in the rat.

**4) Subchronic Toxicity Study in the Rat**

**Citation**: Tisdel, M. (1983) Thirteen-week Subchronic Study in Rats with EPTC: Final Report: Study No. 6100-105. Hazleton Laboratories America, Inc., MRID No.: 00144651, Unpublished

**Executive Summary:** In this subchronic toxicity study (00144651), CD-Crl:CD (SD)BR rats (20/sex/dose) were fed diets containing EPTC (98.4%) at 0, 18/3, 36/15, 72, or 120 mg/kg/day. When it became apparent to the study director that a NOAEL for body weight may not be achieved after six weeks of treatment, the two lowest doses were reduced to 3 and 15 mg/kg for the remainder of the study (weeks 7 to 13).

No treatment-related deaths or clinical signs were observed during the study. Mean body weights at week 6 (just prior to dose reduction) were significantly reduced at 18, 36, 72, and 120 mg/kg/day in males (8, 11, 13, and 17%, respectively) and females (7, 10, 10, and 9%, respectively). At week 13, statistically significant decreases in body weights were observed at 15, 72, and 120 mg/kg/day in males (10, 15, and 19%, respectively) and females (9, 11, and 13%, respectively). For weeks 0 to 6, body weights gains were significantly decreased at 8, 36, 72, and 120 mg/kg/day by 13, 17, 20, and 29%, respectively, in males and by 16, 25, 25, and 23%, respectively, in females. Following the reduction in dose at week 7 through the remainder of the study, body weight gains were statistically significantly decreased from control values only at 72 mg/kg/day (20%, males; 14%, females) and 120 mg/kg/day (17%, males; 24%, females). Overall (weeks 1 to 13) body weight gains were statistically significantly decreased from control values at 36/15, 72, and 120 mg/kg/day in males (13, 21, and 26%, respectively) and females (11, 12, and 12%, respectively). Food consumption was consistently decreased in males at 36 mg/kg/day (through week 6) and males and females treated at 72 and 120 mg/kg/day for the entire study. Food consumption by males at 36, 72, and 120 mg/kg/day during the first 6 weeks of treatment, but not after the reduction in dose at week 7.

At week 13, clinical pathology results showed treatment-related changes in clinical chemistry parameters in animals dosed at 72 and 120 mg/kg/day. Hematology findings were not affected by treatment. Blood urea nitrogen concentrations were significantly increased over control values at 72 mg/kg/day (135%, males; 148%, females) and 120 mg/kg/day (136%, males; 153%, females). Blood glucose concentrations were significantly decreased in females at 72 mg/kg/day

(88% of control) and 120 mg/kg/day (77% of control). Aspartate aminotransferase (AST) activity was greater than control values at 72 mg/kg/day (207%, males; 149%, females) and 120 mg/kg/day (237%, males; 196%, females). Brain cholinesterase (ChE) activity was also significantly decreased by 14% in high-dose females. Plasma, blood and brain ChE activities in low-, mid-, and high-dose males and low- and mid-dose females were comparable to control values.

Necropsy evaluations revealed treatment-related changes in organ weights. Absolute hearts weights were significantly ($p \leq 0.05$) decreased in males treated at 36/15 mg/kg/day (1.36 g) and 120 mg/kg/day (1.34 g) compared to the control value (1.47 g). Relative heart weights (as % of terminal body weight) in males were significantly ($p \leq 0.05$) increased at 72 mg/kg/day (0.33%) and 120 mg/kg/day (0.34%) compared to the control value (0.30%). Organ weights of males treated at 18/3 mg/kg/day and all treated females groups were comparable to control values.

Histopathological evaluation revealed a dose-related increase in the incidence and severity of chronic myocardial inflammation. The inflamation was described as focal to multifocal degeneration with infiltrating mononuclear cells, fibroplasia and occasional fatty changes. While no myocardial inflammation was noted in control males, treatment-related findings were observed in males dosed at 18/3 mg/kg/day (1/19, slight), 36/15 mg/kg/day (5/20, slight; 1/20, minimal), 72 mg/kg/day (5/20, slight; 5/20, minimal), and 120 mg/kg/day (1/20, slight; 6/20, minimal; 9/20, marked; and 4/20, severe). For females no myocardial inflammation was observed in control and low-dose groups, while increases were noted at 36/15 mg/kg/day (2/20, slight), 72 mg/kg/day (3/20, slight; 10/20, minimal; 2/20 marked) and 120 mg/kg/day (4/20, slight; 2/20, minimal; 3/20 marked).

Based on the results of this study (decreased body weight and body weight gain and increased incidence of cardiomyopathy), the LOAEL was established at 15 mg/kg/day in males and females. The NOAEL was established at 3 mg/kg/day in males and females.

The cholinesterase LOAEL was established at 120 mg/kg/day based of 14% inhibition of plasma ChE in females and not established in males. The NOAEL was established at 72 mg/kg/day in females and 120 mg/kg/day in males.

This study is acceptable (guideline), and satisfies requirements (§82-1) for a subchronic toxicity study in the rat.

**5) Subchronic Toxicity (Feeding) Study in the Dog**

**Citation**: Daly, I. (1985), A Three Month Subchronic Oral Dietary Toxicity Study of EPTC in Beagle Dogs: Project No. 83-2781, Bio/Dynamics Inc., MRID No.: 00150327, HED Doc No.: 5190, Unpublished

**Executive Summary**: In this subchronic study (00150327), dogs (6/sex/dose) were fed diets containing EPTC (98.4%) at 0, 200, 600, or 1800 ppm (equivalent to approximately 0, 5, 15 or 45 mg/kg/day) for three-months.

Except for consistently excessive salivation in one high-dose male, no other clinical signs considered to be treatment-related were observed in any of the test animals throughout the study.

Mean body weights of high-dose males were consistently lower than control values throughout the study and were attributed to emaciation (of unknown cause) in two animals. One low-dose male was also emaciated during the 13 weeks of treatment, but its weight loss did not significantly skew the mean value for the group. Transient decrease in food consumption was observed in high-dose males and females on day 1, and was attributed to initial palatability of the test diet. During the remainder of the study, food consumption of high-dose females increased to control levels, while that of the males remained slightly reduced.

Except for hypertrophy and prolapse of the third lid of the right eye of one mid-dose male (considered a common lesion in Beagles), no ocular abnormalities attributable to treatment were recorded.

Treatment-related changes were observed in some of the clinical chemistry, but not hematology, parameters. Blood urea nitrogen (BUN) levels were increased in the two high-dose emaciated males. Mean plasma ChE activity of high-dose males was slightly, but significantly, decreased (about 25% of control value) at week 7 and at termination. Plasma, blood and brain ChE activities of other males and female treatment groups were comparable to control values.

No gross, organ weight, or histopathological changes were found in EPTC-treated animals.

The LOAEL for systemic toxicity was established at 1800 ppm (45 mg/kg/day) based on excess salivation and decreased body weight in males; the LOAEL was not established in females. The NOAEL was established at 600 ppm (15 mg/kg/day) in males and 1800 ppm (45 mg/kg/day) in females.

Based on decreased plasma ChE activity (25%) in males, the LOAEL for ChE inhibition was established at 1800 ppm (45 mg/kg/day); the LOAEL was not established in females. The NOAEL was established at 600 ppm (15 mg/kg/day) in males and 1800 ppm (45 mg/kg/day) in females.

This study is acceptable (guideline) and fulfills requirements [§82-1(b)] for a subchronic toxicity study in the dog.

**6) Subchronic Inhalation Study in the Rat**

**Citation**: Scott, J. (1985) Subchronic Inhalation Toxicity of EPTAM in Rats: T-10422., Stauffer Chemical Co., MRID No.: 00154784, Unpublished

**Executive Summary**: In this subchronic inhalation study (00154784), Sprague-Dawley rats (24/sex/dose, 7 to 8 weeks old) were exposed in a whole body chamber to aerosolized [particle size, MMADar = 2.8 μm] EPTC (98.6%) at concentrations of 0, 8.3, 58 or 290 mg/m$^3$, six 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 increased incidence in mid- and high-dose animals. These clinical signs consisted of ocular irritation, chromodacyorrhea, and alopecia.

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. At the high-dose level, AST activity was significantly increased by 153% in females. At 7 weeks, brain ChE was inhibited in high-dose males (15%) and in females (13%). At study termination, brain ChE activity was decreased in low- mid- and high-dose males (13%, 20%, and 18%, respectively) and mid- and high-dose females (16% and 20%, 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 revealed increased incidence of cardiomyopathy in all (24/24) high-dose males and females. Although the heart lesions are probably treatment-related, the results are confounded by increased incidence in control males (17/24) and females (18/24), as well as low-dose (7/23, males; 14/24, females), and mid-dose (20/24, males; 14/24, females) animals.

Based on the results of this study (clinical signs, decreased food consumption, brain ChE inhibition in males, and increased prothrombin time in females), the LOAEL was established at 58 mg/m$^3$. The NOAEL was established at 8.3 mg/m$^3$.

This study is acceptable (guideline) and satisfies requirements (§82-4) for a subchronic inhalation study in the rat.

**25) Subchronic Neurotoxicity Study in the Rat:**

**Citation:**

Tinston, D. (1994) EPTC: Subchronic Neurotoxicity Study in Rats: Lab Project Number: CTL/P/3930: PR0929, Zeneca Central Toxicology Lab., UK, MRID No.: 43230901, HED Doc No.: 011311, Unpublished.

Tinston, D., First Revision to EPTC: Subchronic Neurotoxicity Study in Rats, Addendum to 43230901, Lab Project Number: CTL/P/3930: PR0929, Zeneca Central Toxicology Lab., UK, MRID No.: 43964401, Unpublished.

Chalmers, D.J., Duffel, S.J., and Horner, S.A., Thiocarbamates: Selective Re-examination of Neuropathology, Report No. CTL/P/4618, Study No.: PR0999, Zeneca Central Toxicology Laboratory, UK, March 28, 1995, MRID No.: 43948301, Unpublished.

**Executive Summary**: In this subchronic neurotoxicity study (43230901), 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; all other animals survived to terminal sacrifice Urine incontinence was observed in 5/12 high-dose females; no other treatment-related clinical signs were observed.

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 (8 to 14%) and females (10 to 18%). 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 (decreased body weight gain and relative brain weight in females and neuronal necrosis in the brain in males and females), the LOAEL was established at 500 ppm (39 mg/kg/day, males; 44 mg/kg/day, females). The NOAEL was established at 100 ppm (7.9 mg/kg/day, males; 8.8 mg/kg/day, females).

This study is acceptable (guideline) and satisfies the requirements (§82-5b) for a subchronic neurotoxicity study in the rat.

## 8) Combined Chronic Toxicity/Oncogenicity Study in the Rat

**Citation:** Warner, M. (1983) Two Year Oral Toxicity/Oncogenicity Study in Rats with R-1608, International Research and Development Corp., Study No.: T-10001, MRID No.: 00145004, Unpublished

**Executive Summary**: In this combined chronic toxicity and oncogenicity study (00145004, 00145311), Charles River CD rats were fed diets containing sufficient EPTC (purity not given) to yield 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). The amount of EPTC in the diets was varied to achieve the desired dose levels.

Treatment-related clinical signs were observed primarily in high-dose animals. After 85 to 95 weeks of treatment, females, followed shortly thereafter by males, exhibited hindquarter weakness (inability to assume an upright stance). Of the high-dose males in the main study, 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 their control values. Other clinical observations in high-dose males included an increased incidence of cataracts (13/23 vs. 2/28 for controls) and discolored urine.

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 AST were increased in high-dose males and females. Erythrocyte ChE activities were significantly decreased in high-dose males and females; no treatment related changes in brain or plasma ChE activities were seen.

Histopathological examination revealed treatment-related myocardial and neuromuscular lesions. The myocardial lesions were described as atrophied, chronic myocarditis, endocarditis, fibrosis, pericardial chronic inflammation, mineralization, pigmentation, and thrombosis. At the high-dose level, myocardial lesions correlated with increased AST activities. The overall (unscheduled plus scheduled deaths) incidence of all cardiac lesions for the entire study in the control, low-, mid- and high-dose groups was 24/60 (40%), 18/60 (30%), 26/60 (43%) and 38/60 (63%) for males, respectively, and 8/60 (13%), 8/60 (13%), 7/60 (12%), and 39/60 (65%) for females, respectively. Neuromuscular lesions were described as degeneration/atrophy of fore- and hind-limb skeletal, increased incidence of axonal degeneration in the peripheral (sciatic and tibial nerves) and central (lumbar spine) nervous systems. Mid- and high-dose groups which died during the second year of the study and those at terminal sacrifice had high incidences of neuromuscular lesions. For mid-dose animals and high-dose animals, atrophy and degeneration

of muscle adjacent to sciatic nerve in males [31/47 (66%) and 37/39 (95%), respectively, vs. 1/46 (2%) for control] and females [13/50 (26%) and 34/43 (79%), respectively, vs. 0/47 (0%) 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 (80%) and 33/38 (87%), respectively, vs. 10/44 (21%) for control] and mid- and high-dose females [31/38 (82%) and 38/43 (88%), respectively, vs. 7/46 (15%) for control]. Similar effects 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 (85%) and 25/38 (66%), respectively, vs. 21/47 (45%) for control] and mid- and high-dose females [38/50 (76%) and 35/48 (73%), respectively, vs. 8/47 (17%) for control]. A lower incidence of axonal degeneration was noted in the sacral spinal cords of mid- and high-dose males [5/41 (12%) and 7/38 (18%), respectively, vs. 0/46 (0%) for control] and mid- and high-dose females [3/47 (6%) and 9/40 (23%), respectively, vs. 0/39 (0%) for control]. The incidence of axonal degeneration in the thoracic spinal cords of treated animals were similar to control values.

There was no evidence that EPTC increased the incidences of neoplastic lesions.

Based on the results of this study (decreased body weight and increased incidences of myocardial and neuromuscular lesions), the LOAEL was established at 25 mg/kg/day in males and females. The NOAEL was established at 5 mg/kg/day.

This study is acceptable (guideline), and satisfies requirements (§83-1 and §83-2) for a combined chronic toxicity/oncogenicity study in the rat.

**9) One-Year Chronic Toxicity (Feeding) Study in the Dog:**

**Citation**: Dickie, B. (1986), One-year Oral Feeding Study of the Chronic Toxicity of EPTC in Dogs: Final Report: Study No. 6100-109, Hazleton Laboratories America, Inc., MRID No.: 00161595, HED Doc No.: 005740, Unpublished.

**Executive Summary:** In this chronic toxicity study (00161595), Beagle dogs (6/sex/dose) were fed diets containing 0, 200, 600, or 1800 ppm (equivalent to 0, 5.6, 17.3, or 48.5 mg/kg/day in males and 0, 6.1, 17.4 or 54.7 mg/kg/day in females) EPTC (98.4%) for one-year.

Clinical evaluations did not reveal any overt signs of toxicity, however, little or no feces was observed in mid- and high-dose males (2/6 and 3/6, respectively) and females (1/6 and 3/6, respectively) during the first week of testing. No treatment-related changes were observed in either the electrocardiographs (EKG), ophthalmological, or neurological evaluations.

Statistically significant decreases in mean body weights were observed only in mid-dose males (10 to 12% of control); females were unaffected. Since no dose-response relationship existed, the effects were not considered to be treatment-related. Food consumption of treated animals was comparable to control values.

No treatment-related changes were observed in hematology, clinical chemistry or urinalysis

results. Although sporadic statistically significant differences in clinical chemistry parameters were observed, none were considered biologically significant. ChE activities were unaffected by treatment.

At terminal sacrifice, no toxicologically significant changes in the incidence of gross and histopathological lesions were observed. In high-dose animals, absolute and relative testicular and left thyroid gland weights were decreased in males, and absolute and relative pituitary weights in females. Since these tissues did not show any histopathological changes, the differences in weights were considered unrelated to treatment.

The LOAEL for this study was not established; the NOAEL was established at 1800 ppm (48.5 mg/kg/day, males; 54.7 mg/kg/day, females).

This study is unacceptable (guideline), and does not satisfy requirements [§83-1(b)] for a chronic toxicity study in the dog (LOAEL for study not achieved).

**10) Chronic Oral (Capsule) Toxicity Study in the Dog:**

**Citation**: Sprague, G.; Taylor, D. (1987) One-year Oral Toxicity Study with Eptam Technical in Dogs: T-12723: Final Report. Stauffer Chemical Co., MRID No.: 40442301, HED Doc No.: 006797, Unpublished

**Executive Summary:** In this chronic toxicity study (40442301), Beagle dogs were dosed (capsule) at 0, 1, 8 or 60 mg/kg/day EPTC (97.6%) for one-year. Five animals /sex were assigned to control and high-dose groups, while four animals/sex were assigned to the low- and mid-dose groups.

One high-dose male showed signs of anorexia, ataxia, dull fur coat, muscle fasciculations, reduced activity, stiff gait in the hind limbs, and weakness in the front limbs before being sacrificed *in extremis* on day 84. All other animals survived to terminal sacrifice with minimal clinical signs in mid- and high-dose animals. Erythema of the ears was observed in mid- and high-dose males (3/4 and 3/5, respectively) and dull fur coat in high-dose males (2/5) and females (1/5) and mid-dose females (1/4). Stiff gait in the hindlimbs was observed in 2/5 high-dose females. Despite the effects observed during the clinical exams, no abnormalities were noted during the neurological examinations. One high-dose male had changes in the EKG which were described as "potentially" treatment-related.

Body weights and food consumption of treated animals were comparable to control values throughout the study. Compared to the body weight gain of 1.7 kg for control males, high-dose males gained only 0.1 kg during the entire 52-week study.

Clinical pathological examinations revealed some treatment-related changes in both the hematological and clinical chemistry parameters. Hemoglobin concentration, hematocrit, and erythrocyte count were reduced slightly, but significantly, in high-dose males. Alkaline phosphatase activities were increased in males (1.5 to 2.5-fold higher than controls) and females

(1.4 to 2.6-fold higher than controls). Significant increases were noted in serum cholesterol levels of high-dose females, while BUN levels were decreased in high-dose males (significant) and females (non-significant). At the high-dose level, serum ChE activity was inhibited by 32 to 42% in males (entire study) and 23 to 26% in females (months 1 and 12 only). No treatment-related decreases were noted in brain and erythrocyte ChE activities.

Treatment-related necropsy findings were limited to high-dose animals. Increased relative (females) and absolute (males) liver weights were observed in high-dose animals, but, the lack of supporting histopathological findings suggests that the effects were adaptive, rather than treatment-related. Gross findings of the high dose male which was sacrificed revealed muscle atrophy; gross findings of other treated animals were similar to controls.

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 (all levels) and various peripheral nerves (sciatic, sacral, and tibial nerves). The male which was sacrificed early 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. Other possible treatment-related effects included mild thymic atrophy was observed two high-dose males, one mid-dose male and one low-dose female and mild bile stasis in the livers of high-dose males (4/5 vs. 1/5 for control). Additionally, small foci of alveolar fibrosis, accompanied by chronic inflammation, were found in the lungs of high-dose males (2/5), and all treated females (1/5, low-dose; 3/4, mid-dose; 2/5, high-dose vs. 1/5 for control).

Based on the results of this study (decreased body weight gain in males and peripheral/central nervous system degeneration and skeletal/cardiac muscle degeneration in males and females), the LOAEL of this study was established at 60 mg/kg/day. The NOAEL was established at 8 mg/kg/day.

The LOAEL for ChE inhibition (decreased plasma ChE by 32 to 42% in males and 23 to 26% in females) was established at 60 mg/kg/day. The NOAEL for ChE inhibition was established at 8 mg/kg/day.

This study is acceptable (guideline) and satisfies requirements [§83-1(b)] for a chronic toxicity study in the dog.

**11) Oncogenicity Study in the Mouse**

**Citation**: Tisdel, M. (1985) Oncogenicity Study in Mice with EPTC: Final Report: Study No. 6100-104, Hazleton Laboratories America, Inc., MRID No.: 00161596, HED Doc No.: 005740, Unpublished

**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.

No treatment-related clinical signs were observed during the study. Mortality of treated animals was comparable to control values.

At the high-dose level, consistent and statistically significant ($p \leq 0.05$) decreases in body weights of 3 to 13% in males and 10 to 13% in females. At the mid-dose level, 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.

No treatment-related differences were noted in any of the hematological parameters evaluated. Clinical chemistry and urinalysis were not performed.

Pathological evaluation did not reveal any treatment-related macroscopic effects; the lesions were not considered unusual in type, frequency, or severity. The incidence of non-neoplastic microscopic lesions were similar between control and treated mice.

There was no evidence of carcinogenicity attributed to EPTC. 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. The doses used in this study were adequate to assess the oncogenic potential of EPTC.

Based on the results of this study (decreased body weight and food consumption), the LOAEL was established at 1800 ppm (270 mg/kg/day). The NOAEL was established at 600 ppm (90 mg/kg/day).

This study is acceptable (guideline) and satisfies requirements (§83-2a) for an oncogenicity study in the mouse.

**12) Developmental Toxicity Study in the Rat:**

**Citation:** Nemec, M.; Rodwell, D.; Kopp, S.; et al. (1983) A Teratology Study in Rats with EPTAM: Project No. WIL-27013; T-11753. Final rept. WIL Research Laboratories, Inc, MRID No.: 00138919, Unpublished

**Executive Summary**: In this developmental toxicity study (00138919), 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.

No deaths occurred in the control, low- or mid-dose groups, while in the high-dose group, 14 deaths occurred between GD 11 and 17 (one of these deaths was attributed to dosing error). Of

the treatment-related deaths, high incidences of "metrorrhagia", severe internal hemorrhage, or cardiorespiratory arrest were observed at necropsy evaluation. Clinical signs were observed on GD 7 in all high-dose animals and consisted of wet, matted, stained urogenital region and red matter in the facial area and/or various other body surfaces. No treatment-related clinical signs were observed in low- or mid-dose animals.

Body weights and body weight gains were adversely affected in the high-dose group. Mean body weights were decreased by 12% on GD 16 and 17% on GD 20 when compared to control values. During GD 6 to 16 high-dose animals lost an average of 17 g, compared to a gain of 34 g by control animals. During the entire gestation period, body weight gain by high-dose animals was 39% lower than the control. Adjusted mean body weight (total maternal body weight - gravid uterine weight) was also significantly deceased in the high-dose group (13.6 g vs. 33.8 for control). Food consumption by high-dose animals 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 deaths in the high-dose group resulted in only six litters with viable fetuses surviving to scheduled sacrifice; litter sizes of 22, 19, and 21 were obtained in the control, low- and mid-dose groups, respectively. Post-implantation loss per 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. The reduction was 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 per dam, respectively, the number of corpora lutea to be 11.1 per dam, and the number of normal implants to be 7.3 per dam. Mean fetal body weight of high-dose litters was significantly reduced (2.8 g vs 3.4 g for control). In control, low-, mid- and high dose groups, the percent of malformed fetuses was 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%, 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 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.

Based on the results of this study (lethality, decreased body weight, body weight gain, corrected body weight gain, and food consumption), the LOAEL for maternal toxicity was established at 300 mg/kg/day; the NOAEL was established at 100 mg/kg/day.

Based on the results of this study (decreased fetal body weight, decreased litter size, increased resorptions, increased incidence of omphalocle and increased incidence of unossified sternebrae), the LOAEL for developmental toxicity was established at 300 mg/kg/day; the NOAEL was established at 100 mg/kg/day.

This study is classified as acceptable (guideline) and satisfies requirements (§83-3) for a developmental toxicity study in the rat.

### 13) Developmental Toxicity Study in the Rabbit

**Citation**: Gilles, P. (1987) A Teratology Study in Rabbits with Eptam Technical: T-12982: Final Report, Stauffer Chemical Co., MRID No.: 40442302, Unpublished

**Executive Summary**: In this developmental toxicity study (40442302), pregnant New Zealand White rabbits (16/dose and 18/high-dose) were dosed with EPTC (97.6%) at nominal doses of 0 (vehicle, corn oil), 5, 40, or 300 mg/kg/day (achieved doses: 0, 10.3, 75.8, or 568 mg/kg/day, respectively) from 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), loss of appetite/anorexia (12/18). Two high-dose animals died on GD 20, while one control doe died on GD 23. All pregnant surviving animals had live fetuses, and no animals aborted.

Mean body weights and corrected body weights of treated animals were comparable to control values. Mean body weight gain by high-dose animals was significantly reduced on GDs 13 and 19. The decreases in body weight were attributed to six adversely affected animals in this dose group which had extended periods of little or no food consumption during GD 13 through 20.

Serum and erythrocyte ChE activities were statistically significantly (all $p \leq 0.05$) decreased in all treatment groups. Serum ChE activity was inhibited by 10%, 18% and 56% in the low-, mid-, and high-dose groups, respectively, and erythrocyte ChE, by 14% and 70% in the mid-dose and high-dose groups, respectively.

At termination of the study, organ weights (absolute and relative) and necropsy findings of treated animals were comparable to control values. The two high-dose animals which died on study had gross changes which would suggest bleeding within the reproductive tract (both of these animals had hairballs).

Changes in intrauterine finding were generally limited to high-dose animals. At the high-dose level, mean fetal body weight was significantly decreased by 13% (35.3 g *vs.* 40.3 g for control, $p \leq 0.05$). The percent of malformed fetuses (7.4% vs. 2.4% for control) and affected implants (13.1% vs. 5.0% for control) were increased in high-dose animals. In the mid- and high-dose groups, the percent of post-implantation losses (7.2% and 6.2%, respectively) was greater than that of the controls (2.8%). However, 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 statistically significant increases in external, visceral, and skeletal anomalies were observed in any of the treatment groups. Litters of three of the adversely affected animals 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.

Based on the results of the study (inhibition of serum ChE by 10%), the LOAEL for maternal ChE inhibition was established at ≤ 5 mg/kg/day, the NOAEL was not established.

Based on the results of the study (decreased body weight and food consumption, mortality and clinical signs), the LOAEL for maternal systemic toxicity was established at 300 mg/kg/day, the NOAEL was established at 40 mg/kg/day.

Based on the results of this study (reduced fetal body weights), the LOAEL for developmental toxicity was established at 300 mg/kg/day, the NOAEL was established at 40 mg/kg/day.

This study is acceptable (guideline) and satisfies requirements [§83-3(b)] for a developmental toxicity in the rabbit.

**14) Two-Generation Reproduction in the Rat**

**Citation**: Minor, J.; Downs, J.; Zwicker, G.; et al. (1982) A Two-generation Rat Reproduction Study with Eptam Technical: T-10123, CDL: 249077-A, MRID No.: 00121284, Unpublished

Zwicker, G.; Minor, J. (1987) A Two-generation Rat Reproduction Study with EPTAM Technical: T-10123: Addendum to Final Report--Histopathology. Stauffer Chemical Co., MRID No.: 40420408, Upgrade to 00121284, HED Doc No.: 006797, Unpublished

**Executive Summary**: In this two-generation, two-litter reproduction study (0012128, 40420408) 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).

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 (8 to 13%) 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 11 to 12% during gestation and 11 to 14% during lactation. Terminal body weights were significantly decreased in $F_0$ males (7%) and females (10%) and $F_1$ males (18%) and females (15%). In addition to the observed decreases in body weights, food consumption was also decreased.

No treatment-related effects were noted in any of the reproductive and survivability indices parameters of parental for either mating or generation. Pup survival indices for the treatment groups were comparable to controls values. Mean body weights of $F_{1a}$, $F_{1b}$ and $F_{2a}$ high-dose pups were statistically significantly decreased lactation days 14 and 21. Terminal body weights were also significantly decreased in both the $F_{1a}$ (males, 15%; females, 18%) and $F_{1b}$ (males, 10%; females, 9%) weanlings. Non-significant decreases in terminal body weights were

observed in $F_{2b}$ males and females 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 in $F_0$ females and $F_1$ males and females; this lesion was present in treated $F_0$ males, but the incidence (12/15 to 13/15) was not significantly different from that of the control (8/15). The severity of the lesion increased from minimal to slight 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. 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, $p \leq 0.01$).

The LOAEL for parental systemic toxicity was established at 1000 ppm (50 mg/kg/day), based on degenerative cardiomyopathy in males and females and renal tubule degeneration in females; the NOAEL was established at 200 ppm (10 mg/kg/day).

The LOAEL for reproductive toxicity was not established (> 1000 ppm, > 50 mg/kg/day); the NOAEL was established at 1000 ppm (50 mg/kg/day).

The LOAEL for developmental toxicity was established at 1000 ppm (50 mg/kg/day) based on decreased pup weight during postnatal day 14 to 21; the NOAEL was established at 200 ppm (10 mg/kg/day).

This study is acceptable (guideline) and satisfies requirements (§83-4) for a two-generation reproduction study in the rat.

**15) Two-Generation Reproduction in the Rat**

**Citation:** Giesler, P.J., Tisdel, M., and Mackenzie, K. (1986) Two-generation Reproduction Study with EPTC in Rats: Report: Study No. 6100-108. study prepared by Hazleton Laboratories America, Inc., MRID No.: 00161597, Unpublished

**Executive Summary:** In this two-generation, two litter reproduction study (MRID 00161597) 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 (7 to 12%, weeks 8 to 23) and females (9%, weeks 8 to 12) and in $F_1$ males (13 to 20%, weeks 0 to 23) and females (7 to 12%, weeks 0 to 12). During GD 0 to 20, the body weights of $F_0$ females were decreased by 6 to 9% and of $F_1$ females, by 11 to 13%. During lactation, body weights of $F_0$ females were decreased by 11% only on day 0, while that of $F_1$ females was decreased by 9 to 14% 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 for $F_1$ adult was 4/25, 3/25, 15/25 and 25/25 for 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. The 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 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.

The parental systemic LOAEL was established at 200 ppm (10 mg/kg/day) in males and females, based on decreased body weight/body weight gain and cardiomyopathy, the NOAEL was established at 50 ppm (2.5 mg/kg/day).

The LOAEL for developmental toxicity was established at 800 ppm (40 mg/kg/day) based on decreased mean pup weight during lactation days 4 to 21. The NOAEL was established at 200 ppm (10 mg/kg/day).

The LOAEL for reproductive toxicity was not established (> 40 mg/kg/day). The NOAEL was established at 800 ppm (40 mg/kg/day).

This study is classified as acceptable (guideline) and satisfies requirements (§83-4) for a two-generation reproduction study in the rat.

**16) Mutagenicity**

**Citation**: Shirasu, Y.; Moriya, M.; Miyazawa, T. (1978) Mutagenicity Testing on EPTC in

Microbial Systems, Study No.: T6617, The Institute of Environmental Toxicology. MRID No.: 00152451, Unpublished

**Executive Summary**: 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.

This study is acceptable (guideline) and satisfied requirements (§84-2) for a mutagenicity study.

**17) Mouse Lymphoma Assay**

**Citation:** Majeska, J., Hertzel, K., and Matheson, D.W. (1984) Mutagenicity Evaluation in Mouse Lymphoma Multiple Endpoint Test Forward Mutation Assay: Report No. T-11907, Stauffer Chemical Co., MRID. No.: 00152454, Unpublished

**Executive Summary**: 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.

This study is acceptable (guideline) and satisfies requirements (§84-2) for a mutagenicity assay.

**18) Mouse Micronucleus Assay**

**Citation**: Majeska, J. (1984) Mutagenicity Evaluation in Bone Marrow Micronucleus: Report No. T-11906. Stauffer Chemical Co., Environmental Health Center., MRID No.: 00142895, Unpublished

**Executive Summary**: In this study (00142895), the mutagenic potential of EPTC (98.6%) was

evaluated in a bone marrow micronucleus assay in the mouse. Male and female mice were orally gavaged with EPTC at doses of 0 (corn oil), 250, 500, or 1000 mg/kg in one trial an at doses of 0, 1000, 1200, or 1400 mg/kg in another. Animals were sacrificed 24, 48, and 72 hours after dosing. Positive control mice were treated with cyclophosphamide.

There were no significant increases in micronuclei at any dose or time group of either sex. No increase in induction of micronuclei with EPTC, administered at toxic levels (reduction in survival by 45%).

This study is acceptable (guideline) and satisfies requirements for a mutagenicity assay (§84-2).

**19) Mouse Lymphoma Assay**

**Citation**: Majeska, J. (1984) Mutagenicity Evaluation in Mouse Lymphoma Multiple Endpoint Test Cytogenetic Assay: Report No. T-11908, Stauffer Chemical Co. MRID No.: 00152455, Unpublished

**Executive Summary**: 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.

This study is acceptable (guideline) and satisfies requirements for a mutagenicity assay (§84-2).

**20) *In vitro* Chinese hamster ovary (CHO) cell chromosome aberration assay**:

**Citation**: Ivett, J. (1985) Clastogenic Evaluation of EPTC Technical, 518-996 BR85-40 in an in vitro Cytogenetic Assay Measuring Chromosomal Aberration Frequencies in Chinese Hamster Ovary (CHO) Cells: Final Report, Project No. 20990, Genetics Assay No. 8031, Litton Bionetics, Inc. , 00161601, Unpublished

**Executive Summary** 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.

This study is acceptable (guideline), and satisfies requirements (§84-2) for a mutagenicity study

**21) Sex Linked Recessive**

**Citation:** Woodruff, R.; Mason, J.; Valencia, R; et al. (1985) Chemical mutagenesis testing in Drosophila. v. results of 53 coded compounds tested for the National Toxicology Program. Environmental Mutagenesis 7:677-70, MRID No.: 00153248, Published

**Executive Summary**: 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 intraabdominally 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. The frequency of lethals in the progeny from EPTC-fed males was 7/5531 (0.13%) and from injected flies, 7/5048 (0.14%).

This study is acceptable (nonguideline)

**22) DNA Damage/Repair**

**Citation**: Bakke, J.; Mirsalis, J. (1986) Evaluation of the Potential of Ethyl-(N,N-dipropyl) Thiocarbamate To Induce Unscheduled DNA Synthesis in Primary Rat Hepatocyte Cultures: Final Report: SRI Project LSC-8644. MRID No.: 00161600,Unpublished

**Executive Summary**: 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 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).

This study in acceptable (guideline), and satisfies requirements for *in vitro* mutagenicity in rat hepatocytes.

**23) Mouse Lymphoma Assay**

**Citation:** Rudd, C. (1986) Mouse Lymphoma Cell Mutagenesis Assay (TK+/->TK-/-) of EPTC: Final Report: SRI Project LSU-8644-1, SRI International,.00161602 Unpublished.

**Executive Summary**: In this study (00161602), EPTC (98.5%) was evaluated in a mouse lymphoma cell metagenesis assay ($TK^{+/-}$ +$TK^{-/-}$) with or without metabolic (S9) activation.

In the absence of S9 activation, no increase in mutant colonies over the solvent control value (average mutant frequency of $80/10^6$ cells) was found at any level of EPTC (73 to 123 µg/mL).

**24) Dermal Absorption:**

**Citation:** Jeffcoat, A. (1988) Dermal Absorption of EPTAM in Rats: Lab Project Number: 3586/40. Unpublished study prepared by Research Triangle Institute, MRID No.: 41686201, HED Doc No.: 008258, Unpublished

**Executive Summary**: In this dermal absorption study (41686201), $^{14}C$-labeled EPTC (EPTAM 7E formulation, 77.7% a.i.) was applied to an area of 29 $cm^2$ on the backs of male rats (Crl: CD (SR) BR). The application sites were clipped free of fur, washed with soapy water, rinsed with water and dried 24 hrs prior to dosing. Animals (28/dose) were dosed at 254, 26.1, 5.68 and 2.73 mg/rat. Four rats/dose were sacrificed after 1, 4, or 10 hours of exposure. The remaining 16 rats/dose were exposed for 24 hr, at which time the application sites were cleaned. Four rats/dose were sacrificed immediately after the application site was cleaned and the remaining groups of 4/dose were sacrificed 48, 72 and 96 hrs after dose administration. After dosing, animals were placed in individual metabolism cages; urine and feces were collected at 1 hr, 4 hr, 10 hr, 24 hr, and each subsequent 24 hr period until the animals were sacrificed. Application sites were protected charcoal-impregnated filter and secured with tape.

Total recovery of labeled EPTC ranged from 85 to 100%, with most of the radioactivity (75% to 85%) evaporating from the skin. For animals dosed at 254, 26.1, 5.68 and 2.73 mg/rat, the total amount of EPTC absorbed was 1.12%, 2.22%, 2.41%, and 2.13%, respectively, after 1 hr of

exposure; 4.73%, 4.29%, 4.02%, and 3.85%, respectively, after 4 hours of exposure; 4.94%, 4.41%, 3.36%, and 4.58%, respectively, after 10 hr of exposure; and 8.59%, 5.75%, 3.06% and 5.59%, respectively, after 24 hours of exposure. The dose-duration of the exposure did not appear to produce a discernable pattern of absorption.

This study is classified as acceptable (guideline), and satisfies requirements (§85-2) for a dermal absorption study in the rat.