RERRO: Still no data gap! (cf: Taylor 05-07-86) CAS NO. 759-94-4

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

004277

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Review of Studies on EPTC: 1) 2-Generation Reproduction Study in Rats; Study No. T-10123 and 2) Teratology Study in Mice; Study No. T-6529
Action #: 476-2140

TO: Robert Taylor
Product Manager (25)
Registration Division (TS-767)

THRU: Christine F. Chaisson, Ph.D. CFC 2/1/85
Head, Review Section IV
Toxicology Branch
Hazard Evaluation Division (TS-769)

FROM: Chad B. Sandusky, Ph.D. Chad B Sandusky 2/1/85
Pharmacologist
Toxicology Branch
Hazard Evaluation Division (TS-769)

Action Requested:

Stauffer Chemical Company has submitted for review a 1) 2-generation rat reproduction study (Study No. T-10123; Accession No. 249077) and 2) a safety evaluation by teratological study in the mouse, (Study No. T-6529, Accession No. 247780). These studies were submitted under Data - Call - In dated October 29, 1981.

Review and Conclusions:

Summary reviews and conclusions of these studies are presented below. Complete data evaluation records are attached, where appropriate.

1) STUDY TYPE: Two-generation reproduction study in rats.

CITATION: Minor, J.L. A two-generation rat reproduction study with Eptam Technical. (Unpublished study No. T-10123 by Stauffer Chemical, Co., Farmington, CT 06032; dated October 8, 1982).

ACCESSION NUMBER: 249077.

LABORATORY: Stauffer Chemical Co., Environmental Health Center, Farmington, CT 06032.

TEST MATERIAL: Eptam Technical; EPTC, eprolate. Amber liquid, Lot No. EHC-0048-01 (CHK0601), to be stored in a cool, dry ventilated location, purity of 98.6% by weight.

PROCEDURES: Sixty male and 120 female 4-6 week old CD® strain rats were used in the study. The rats were quarantined for 13 days prior to selection and study initiation. All rats were individually housed except during mating when one male was housed with two females.

The 60 males and 120 females were divided into 4 dose groups of 15 males and 30 females on the basis of body weight. The groups were fed diets containing 0, 40, 200, or 1000 ppm Eptam. The F_o rats were fed the treated or control diets for 90 days prior to the mating period. After mating and verification of pregnancy (presence of sperm or copulatory plug), the rats were separated. The pregnant females were examined daily for signs of compound toxicity. Pups (F_{1a} litters) were weaned after 21 days and parents remated 5-10 days later for the second litter (F_{1b}). F_{1b} pups selected for the next generation mating were housed together by litter until approximately day 40 of age when they were separated. Fifteen males and 30 females randomly selected per group from each F_{1b} litter were rised (continously on appropriate test diet) to 100 days of age and then mated in the same way as the F_o rats.

Routine toxicity and reproductive indices were monitered on parental, weanling and post-weaning aniamls, including, body weights, food consumption, litter size, number live and dead, gross anomalies, sex of pups, etc. In addition, attention was paid to the development of 5 maturational landmarks during lactation: unfolding of the external pinna of the ear; incisor eruption; opening of the eye; absence of milk in the pup's stomach (determined by unspecified method); and retrieval behavior in the female.

All F_o parents, F_1 parents, 10 F_{1b} and 10 F_{2b} weanlings per sex in each study group, 10 F_{1a} weanlings in the control and high-dose groups, all dead preweaning pups, and all stillborn pups were given a complete necropsy. All litters were culled, at an unspecified time, to 10 rats per litter. The remaining pups were given a partial necropsy.

Selected tissues were fixed for histological examination. No further details were provided. In addition, the following reproductive indices were calculated: fertility (percentage of females having live-born pups); live born (number of

live pups per the total number of pups born); gestation (percentage of positive mating sign matings resulting in the birth of live pups); viability (percentage of total pups born that survive to day 4 of lactation); survival (percentage of live-born pups that survive to days 1, 4, 7, 14, or 21); and lactation (percentage of pups alive on day 4 that survive to weaning).

Results and Conclusions:

There was a reduction in parental body weight (in the high-dose group) which paralled a reduction in food consumption. The similarity of these values suggested that the body weight decrease was due to the decreased food consumption and not an adverse effect of the test compound.

The only observed compound-related toxicological effects were changes in organ weights of adults and weanlings. The parental NOEL for organ weight change, i.e., brain decrease in F_0 and F_1 males and females, was 200 ppm (mid dose), the LEL was 1000 ppm (high dose). However, there was a concomitant decrease in food intake and body weight at the high dose; therefore the toxicological significance of these findings is difficult to evaluate. In addition, pup body weight was decreased by an average of 9.5% at day 21 of lactation for all four matings at 1000 ppm (LEL), but not at 200 ppm (NOEL).

However, based on the data as reported, the effect on reproduction of Eptam administered in the diet could not be properly assessed. While no functional compound-related reproductive effect, i.e., reproductive and pup survivability indices, were observed, the lack of histopatholgical data does not allow a proper evaluation. Therefore, based on these data, a NOEL and LEL for reproduction cannot be established.

CORE CLASSIFICATION: Supplementary.

Additional information requested:

a. Histopathological evaluations which were proposed in the protocal must be performed on reproductive and target (as revealed on Table 2) organs before a proper evaluation of the reproductive effects of EPTC can be made.

b. The definition of "anomalous" gross pup observations needs to be clarified.

c. The authors should explain why the summary table values for "anomalous" pup observations were consistently higher than individual animal data.

2. STUDY TYPE: Teratogenicity Study in Mice (Feeding Study).

STUDY IDENTIFICATION: Beliles, R. P. and Scott, W.J. Eptam-safety evaluation of teratological study in the mouse. (Unpublished Study No. T-6529 prepared by Woodard Research Corporation, Herndon, VA for Stauffer Chemical Company; dated April 6, 1967).

Accession No. 247780

TEST MATERIAL: Eptam Tech 97.8%; Lot No. 8799205; described as a yellow liquid; active ingredient S-ethyl dipropylthiocarbamate.

CONCLUSIONS:

The potential teratogenic effects of the test material (administered by dietary inclusion at concentrations of 0, 53, and 160 ppm) in mice could not be evaluated on the basis of this study due to the following deficiencies:

a. Absence of maternal effects even at the highest level used in this study.

b. Utilization of only two groups dosed with Eptam consisting of 10 mated females (to be delivered by caesarean section) per group. The resulting number of pregnant animals C-sectioned were only 7, 8, and 6 for the 0, 53, and 160 ppm groups, respectively.

c. Homegeneity, stability and concentratin of the test material in the feed was not presented.

d. Maternal food consumption data (which is essential in determining the actual intake of the test material) were not presented. This is essential in a non-gavage teratology study.

d. Absence of individual data for maternal clinical observations, fetal body weights, and external, visceral, and skeletal fetal examinations.

CORE CLASSIFICATION:

Due to the above listed deficiencies, this core study is classified Core Invalid.

CONFIDENTIAL PER ... ION
DOES NOT CONTAIN
NATIONAL SECURITY INFORMATION (EO 12065)

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EPA: 68-01-6561
TASK: 89
January 28, 1985

DATA EVALUATION RECORD

EPTAM

Two-Generation Reproduction Study in Rats

CITATION: Minor, J.L. A two-generation rat reproduction study with Eptam Technical. (Unpublished study No. T-10123 by Stauffer Chemical, Co., Farmington, CT 06032; dated October 8, 1982.)

REVIEWED BY:

Paul Wennerberg, D.V.M., M.S.
Project Scientist
Dynamac Corporation

Signature: Paul Wennerberg
Date: 1-28-85

Finis Cavender, Ph.D.
Senior Scientist
Dynamac Corporation

Signature: Finis Cavender
Date: 1/28/85

I. Cecil Felkner, Ph.D.
Program Manager
Dynamac Corporation

Signature: I Cecil Felkner
Date: 1-28-85

APPROVED BY:

Chad Sandusky, Ph.D.
EPA Scientist

Signature: Chad B. Sandusky
Date: Jan 30, 1985

Christine Chaisson, Ph.D.
EPA Section Head

Signature: CF Chaisson
Date: 2-1-85

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STUDY TYPE: Two-generation reproduction study in rats.

CITATION: Minor, J.L. A two-generation rat reproduction study with Eptam Technical. (Unpublished study No. T-10123 by Stauffer Chemical, Co., Farmington, CT 06032; dated October 8, 1982.)

ACCESSION NUMBER: 249077.

LABORATORY: Stauffer Chemical Co., Environmental Health Center, Farmington, CT 06032.

QUALITY ASSURANCE STATEMENT: Present, signed and dated October 6, 1982.

TEST MATERIAL: Eptam Technical; EPTC, eprolate. Amber liquid, Lot No. EHC-0048-01 (CHK0601), to be stored in a cool, dry ventilated location, purity of 98.6% by weight.

PROCEDURES:

1. Sixty male and 120 female 4-6 week old CD® strain rats supplied by Charles River Breeding Laboratories (Wilmington MA) were used in the study. The rats were quarantined for 13 days prior to selection and study initiation. All rats were individually housed except during mating when one male was housed with two females.

2. A premix was made with Eptam Technical, corn oil, and Purina Certified Rodent Chow #5002. This premix was added to basal feed with corn oil to make the high-dose level of 1000 ppm. This diet was then appropriately mixed with basal feed and corn oil to make the mid-dose level of 200 ppm with the latter then mixed to make the low-dose level of 40 ppm. Each diet contained 1% corn oil. Diets were prepared fresh every 3-5 weeks, stored at room temperature, and used within 6 weeks. Nine samples were taken from each dose level made until October 1980, and then approximately monthly, to test for homogeneity and concentration of test compound.

3. The 60 males and 120 females were divided into 4 dose groups of 15 males and 30 females on the basis of body weight. The groups were fed diets containing 0, 40, 200, or 1000 ppm Eptam. The dietary concentration of Eptam was not adjusted during the study.

F_0 rats were fed the treated or control diets for 90 days prior to the mating period. During the mating period, a daily vaginal smear from females was examined to determine the stage of estrus, evidence of sperm, and/or a copulatory plug. The day evidence of sperm or a copulatory plug was present was considered day 0 of gestation. Upon evidence of mating, or after 7 days, the rats were separated. The pregnant females were examined daily for signs of compound toxicity. Pups (F_{1a} litters) were weaned after 21 days and parents remated 5-10 days later for the second litter (F_{1b}). F_{1b} pups selected for the next generation mating were housed together by litter until approximately day 40 of age when they were separated. Fifteen males and 30 females randomly selected per group from each F_{1b} litter were raised (continously on appropriate test diet) to 100 days of age and then mated in the same way as the F_0 rats.

All cages contained 3/4 to 1 inch of Ab-sorb-dri® wood chip. The temperature was maintained at 65-75° F with a relative humidity of 40-60%. A 12 hour light/dark cycle was maintained with a minimum of 15 room air changes per hour. Animals were allowed control or treated food (Purina Certified Rodent Chow #5002) and water ad libitum.

4. All parental (post-weaning) animals were examined daily for signs of toxicity or ill health. Body weight measurements and food consumption were recorded for the following: all animals during the growth phase; males and unmated females following the mating period; pregnant female body weights during gestation days 0, 6, 13, and 20 with food consumption during days 0-6, 6-13, and 13-20; and female body weights at lactation days 0, 4, 7, 14, and 21 with food consumption during at days 0-4, 4-7, 7-14, and 14-21.

   Litters were examined on lactation days 0, 4, 7, 14, and 21 for total litter size, number live and dead, gross anomalies, weight, and sex of each pup. Attention was paid to the development of 5 maturational landmarks during lactation: unfolding of the external pinna of the ear; incisor eruption; opening of the eye; absence of milk in the pup's stomach (determined by unspecified method); and retrieval behavior in the female.

   All F_0 parents, F_1 parents, 10 F_{1b} and 10 F_{2b} weanlings per sex in each study group, 10 F_{1a} weanlings in the control and high-dose groups, all dead preweaning pups, and all stillborn pups were given a complete necropsy. All litters were culled, at an unspecified time, to 10 rats per litter. The remaining pups were given a partial necropsy.

   The following tissues were fixed for histological examination: 28 tissues (males) and 26 tissues (females) including all reproductive organs from control and high-dose F_0 and F_1 parents; 6 nonreproductive tissues (trachea, esophagus, thyroid plus parathyroid, liver, heart, and adrenals) and the reproductive tracts from low- and mid-dose F_0 parents; 6 nonreproductive tissues plus ovaries or

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testes from 10 F_{1b} and 10 F_{2b} weanlings per sex in the control and high-dose groups.

Absolute and relative organ weights were measured in F_0 and F_1 parents, and in F_{1a}, F_{1b}, and F_{2b} weanlings for the following organs: liver; kidneys; heart; lung; brain; and testes with epididymis.

Tissue samples saved for histopathology were "routinely processed for light microscopic examination" (no specific description given). Pups were fixed in Bouins' fixative with or without 70% alcohol.

The following reproductive indices were calculated: fertility (percentage of females having live-born pups); live born (number of live pups per the total number of pups born); gestation (percentage of positive mating sign matings resulting in the birth of live pups); viability (percentage of total pups born that survive to day 4 of lactation); survival (percentage of live-born pups that survive to days 1, 4, 7, 14, or 21); and lactation (percentage of pups alive on day 4 that survive to weaning.)

5. Enumeration data were evaluated with the Fisher exact test. Other data were evaluated with Mann-Whitney nonparametric rank test and Dunnetts' procedure. All tests were two-tailed with the level of significance at $p < 0.05$. "Animals which were not characteristic of the major portion of the animals, and values which were judged to be outliers were removed and the statistics reported based on this edited subset."

   Unless otherwise specified, the use of the word significant in this report has statistical connotations at $p < 0.05$.

RESULTS:

Clinical Observations: During the study only one adult (F_1 female No. 425) was sacrificed early and had an undiagnosed tumor first seen at 123 days into the study. All the remaining parental animals survived to scheduled sacrifice. No adverse clinical signs were noted in any parental male. An increased incidence of dehydration, edematous ears, masses, and chromodacryorrhea was seen in dosed females and were considered to be not related to treatment.

Body Weight, Food and Compound Consumption: Adult F_0 males showed no treatment-related change in these three parameters during the times measured as listed in the Procedures section. F_1 adult males in the high-dose group showed a significant decrease in body weight (about 16%) and food consumption (about 12%) when compared to controls during the times measured as listed in the Procedures section. See Table 1. A significant decrease in body weight (10%) and food consumption (12%) was noted in the high-dose F_0 females when compared to controls. A 13%

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TABLE 1. Selected[a] Mean Body Weight and Food Consumption Values During Premating, Gestation, and Lactation Periods for Adults Fed Eptam During a Two-Generation Reproduction Study

Generation and Sex	Day of Study	Body Weight (g)	Food Consumption (g)
F_1-males	230	326[b]/282*	27/22*
	273	486/413*	25/22*
	350	581/494*	24/20*
F_0-females	28	226/208*	18/16*
	63	270/242*	17/15*
	90	291/254*	17/15*
F_1-females	230	213/187*	20/16*
	273	276/239*	17/14*
	392	336/294*	19/16*
F_0-females (F_{1b} gestation)	6	322/294*	22.0/17.9
	20	423/384*	23.8/20.8*
F_0-females (F_{1b} lactation)	7	372/321*	51.1/44.9*
	21	356/320*	81.6/67.8*
F_1 females (F_{2b} gestation)	6	338/296*	21.9/17.7*
	20	453/402*	23.5/20.6*
F_1-females (F_{2b} lactation)	7	385/333*	50.8/47.9
	21	364/324*	78.3/73.3*

[a] Selected to show representative significant decreases of high-dose values when compared to controls.

[b] X/Y (X = control, Y = high-dose value).

* Significantly different from control values, $p < 0.05$.

decrease in body weight and a 16% decrease in food consumption was noted for F_1 females when compared to control.

During gestation and lactation, a significant decrease in body weight at each day of measurement as compared to controls was noted for high-dose females in both matings and generations. Food consumption declined during the periods of body weight decrease but was consistently decreased only during the F_1 matings.

Reproductive and Developmental Data and Progeny Survival: No compound-related effects were noted for any reproductive index in either male or female parents for either mating or generation, or for the pup survival indices. These results are summarized on Table 2.

A significant decrease in mean pup weight for lactation days 14 and 21 was noted for the high-dose group in the F_{1a}, F_{1b} and F_{2a} litters when compared to controls. A significant decrease in male mean pup weight was noted in the F_{1b} litters at day 21 in the high-dose group. A few other significant changes were noted but they did not follow a compound-related pattern. No compound-related changes were seen in the occurrence of the developmental landmarks (listed in Procedures).

Macroscopic Necropsy Findings: No significant compound-related macroscopic findings were reported by the study author for pups found dead prior to weaning or sacrificed at weaning.

No compound-related effects were seen in F_0 or F_1 males or females necropsied at study termination.

Organ Weights: There was a significant decrease in the absolute and relative organ weights in the high-dose weanlings and adults when compared to controls for both sexes at all ages and matings (Table 3). The organs included liver, kidney, heart, lung (from author selected F_{1a}, F_{1b}, and F_{2b} weanlings), and brain. The absolute brain weight was the most consistently effected in that it was significantly decreased at the high-dose in all adults and weanlings examined except for the F_{2b} male and female weanlings. The brain-to-body weight ratio was variable. The high-dose group values ranged from nonsignificantly decreased to significantly increased when compared to controls. The F_0 males and females were on the treated diets for approximately 200 days prior to sacrifice and organ weight measurement.

DISCUSSION:

According to Study Author: The author concluded that the only effects attributed to Eptam feeding were parental and fetal body weight and food intake reductions; there were no effects on reproductive parameters. They concluded that the parental effect was due to a toxic reaction to Eptam while the fetal effect was not.

TABLE 2. Summary of Selected Reproductive and Survivability Values and Indices for Rats Fed Eptam During a Two-Generation Reproduction Study

	F_{1a} litters				F_{1b} litters				F_{2a} litters				F_{2b} litters			
Dietary Level (ppm)	0	40	200	1000	0	40	200	1000	0	40	200	1000	0	40	200	1000
No. of females mated	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30	30
No. of females showing signs of parturition[a]					25	25	28	28					29	30	29	30
Fertility index[b]	63	63	70	93	77	73	83	90	93	83	93	90	90	93	73	93
Gestation index[c]	90	86	81	97	100	79	93	96	93	89	97	93	96	100	85	100
Mean litter size at birth	12.9	11.7	13.0	12.3	14.1	13.8	13.0	13.1	14.3	13.9	13.7	13.1	14.2	14.3	15.4	14.1
Liveborn index[d]	99.2	98.3	97.5	98.9	99.1	98.2	98.7	98.8	98.1	99.1	98.3	98.3	97.5	97.6	97.4	97.7
Viability index[e]	97.6	97.9	96.2	97.1	96.7	98.1	97.7	98.0	95.7	98.9	97.2	97.3	96.2	97.4	96.1	96.2
Survival index[f]																
day 1	98.9	100	99.0	100	98.0	100	99	99.5	99.5	99.8	99.7	99.2	99.2	100	99.3	98.4
day 4	98.4	99.6	98.6	98.2	97.6	99.9	99	99.2	97.6	99.8	99.0	98.2	98.6	99.8	98.6	98.4
day 21	98.1	99.6	98.6	97.5	97.1	98.6	99	97.7	96.5	99.1	98.4	97.9	97.5	97.7	97.7	98.2
Lactation index[g]	99.6	100	96.7	99.2	99.6	98.7	100	98.4	98.7	99.2	99.4	98.9	98.9	97.9	99.0	99.7

[a] Determined at necropsy.
[b] percentage of animals that had live born pups.
[c] Percentage of positive matings having the birth of live pups.
[d] Percentage of live pups with respect to the total number born.
[e] Percentage of pups alive on day 4 compared to the total number born.
[f] Percentage of pups alive on the specified day compared to number alive at day 0.
[g] Percentage of pups alive at weaning compared to day 4.

TABLE 3. Selected[a] Mean Organ Weight and Final Body Weight Data for Weanling and Adult Rats Fed Eptam During A Two-Generation Reproduction Study

Generation and Mating	Organ(g)	Dietary Level (ppm) 0	40	200	1000
F_0 adult males	heart	1.77	1.76	1.67	1.62*
	brain	2.32	2.30	2.32	2.25*
	liver-relative[b]	2.4	2.4	2.5	2.7*
	(final body weight)	622	637	634	577*
F_0 adult female	brain	1.98	1.92	1.94	1.77*
	liver-relative	3.7	3.2*	3.3*	4.2*
	kidney-relative	0.68	0.67	0.66	0.75*
	heart-relative	0.40	0.40	0.40	0.46*
	(final body weight)	298	299	296	267*
F_1 adult males	liver	15.7	15.8	15.2	13.4*
	kidney	3.51	3.43	3.34	3.06*
	brain	2.30	2.20	2.22	2.08*
	heart-relative	0.28	0.27	0.27	0.30*
	brain-relative	0.38	0.36	0.37	0.42*
	testes-relative	0.62	0.57*	0.63	0.76*
	(final body weight)	610	635	603	499
F_1 adult female	brain	2.11	2.06*	2.09	1.86*
	liver-relative	2.7	2.6	2.6	3.0*
	kidney-relative	0.59	0.59	0.59	0.67*
	heart-relative	0.36	0.38	0.38	0.41*
	(final body weight)	325	319	318	276*
F_{1a} weanling males	brain	1.77	c	c	1.63*
	heart	0.56			0.51*
	kidney	1.45			1.27*
	liver-relative	5.15			5.90*
	(final body weight)	129.6			110.3*
F_{1a} weanling females	brain	1.72	c	c	1.59*
	lung	0.83			0.68*
	heart	0.51			0.45*
	kidney	1.27			1.05*
	brain-relative	1.50			1.68*
	(final body weight)	116.2			95.3*

TABLE 3. Selected[a] Mean Organ Weight and Final Body Weight Data for Weanling and Adult Rats Fed Eptam During A Two-Generation Reproduction Study (Continued)

Generation and Mating	Organ(g)	Dietary Level (ppm) 0	40	200	1000
F_{1b} weanling males	brain	1.69	1.64	1.68	1.58*
	(final body weight)	82.9	80.1	86.3	74.5*
F_{1b} weanling females	brain	1.65	1.59	1.63	1.49*
	heart	0.40	0.41	0.41	0.36*
	(final body weight)	76.8	75.8	77.6	69.7
F_{2b} weanling males	liver-relative	4.91	4.86	5.17	5.30*
	(final body weight)	67.1	72.9	67.0	72.4
F_{2b} weanling females	liver	2.85	3.39	3.15	3.48*
	lung-relative	0.90	0.98	0.89	0.78*
	heart-relative	0.51	0.49	0.48	0.47*
	liver-relative	4.78	4.96	5.09*	5.28*
	(final body weight)	59.3	67.6	61.8	65.9

[a] Based on the finding of significant change from controls.

[b] Organ weight relative to final body weight.

[c] No data presented in report.

* Significantly different from control value ($p < 0.05$).

According to this Reviewer: The reduction in parental body weight (in the high-dose group) paralled the reduction in food consumption. The similarity of these values suggested that the body weight decrease was due to the decreased food consumption and not an adverse effect of the test compound. We found on data analysis that there were significant changes in high-dose weanling and adult organ weights.

We also found the values listed as "anomalous" findings in the low- and mid-dose F_{1b} pups (13/264, 12/210, and 8/268; low, mid, and high-dose groups, respectively) were significantly increased when compared to controls (4/258) when analyzed by our reviewers using Fisher's exact test. Since the high-dose group was not significantly different from controls, a compound-related effect probably cannot be concluded. However, because the term "anomalous" was never defined and the summary values were consistently higher than the values we derived from individual animal data, the information cannot be verified and evaluated. (See attached Appendices 1-4, F_{1a} mating through F_{2b} mating, respectively). More data are needed before this point can be resolved. We agreed with their conclusion that the decreased high-dose pup weights during lactation probably were not adverse reproductive effects, but may have been due to the decreased maternal body weight and food consumption. The incidence of dehydration in the high-dose F_0 female group (8/30) was significantly different from controls (2/30) when analyzed by us using the Fisher exact test.

The reduction of absolute organ weights in weanlings (except liver in F_{2b} weanling females which increased) could have been compound-related or caused by the decreased food consumption of the dam. The adult organ weight changes, especially the decrease in brain weight, might have been compound related despite the brain-to-body weight ratios not being consistently decreased as would be expected when the effect is toxicological rather than dietary. Our assessment implicates the decreased brain weight in the high-dose group of adults and weanlings as a compound-related effect based on two factors. There was a lack of consistent organ weight decreases in organs expected to decline directly with a decrease in body weight. We agree with the conjecture that the brain barrier provides some protection and would be the last organ normally affected by body weight changes.

Histological data are needed to properly evaluate the points discussed in the preceding paragraph. No parameter involving the reproductive process was assessed to be significantly affected based on the data presented. However, evaluation of the reproductive organs relative to histological data are necessary before a definite conclusion can be made.

In summary, the only probable compound-related effect demonstrated in this study was a significant change in organ weights of adults and weanlings at the high dose. There were other isolated changes at lower doses which were considered not to be compound related.

There are a number of deficiencies that impact on the Core Classification of this study. The major deficiency was that none of the histopathological

exams proposed were actually performed. The report stated that the tissues were kept so they could be examined. Based on the organ weight changes seen, these examinations should be done. As discussed, we were not able to verify the "anomalous" development data in the report authors' summary tables. We also were unable to verify summary data in terms of the number of preweaning deaths when the individual necropsy data were examined. Seventy-one pups died that were not necropsied (see attached Appendices 5-8, F_{1a} mating through F_{2b} mating, respectively).

Reporting deficiencies include the failure to specify whether the same male and female pair was remated for the second mating in each generation and to indicate when the litters were culled.

CONCLUSIONS:

Based on the data reported, the effect of Eptam administered in the diet on reproduction could not be properly assessed. While no functional compound-related reproductive effects, i.e., reproductive and pup survivability indices, were observed, the lack of histopathological data does not allow a full evaluation. Therefore, based on these data, a NOEL and LEL for reproduction cannot be established.

The only observed compound-related toxicological effects were changes in organ weights of adults and weanlings. The parental NOEL for organ weight change, i.e., brain decrease in F_0 and F_1 males and females, was 200 ppm (mid dose), the LEL was 1000 ppm (high dose). However, there was a concomitant decrease in food intake and body weight at the high dose; therefore these findings cannot be adequately evaluated without additional data. In addition, pup body weight was decreased by an average of 9.5% at day 21 of lactation for all four matings at 1000 ppm (LEL), but not at 200 ppm (NOEL).

CORE CLASSIFICATION: Supplementary.

Additional information requested:

1. Histopathological evaluations must be performed on reproductive and target (as revealed on Table 2) organs.

2. The definition of "anomalous" gross pup observations needs to be clarified.

3. The authors should explain why the summary table values for "anomalous" pup observations were consistently higher than individual animal data.

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DATA EVALUATION RECORD

EPTC/EPTAM

Teratogenicity Study in Mice

STUDY IDENTIFICATION: Beliles, R. P. and Scott, W. J. Eptam-safety evaluation of teratological study in the mouse. (Unpublished Study No. T-6529 prepared by Woodard Research Corporation, Herndon, VA for Stauffer Chemical Company; dated April 6, 1967. Accession No. 247780.)

APPROVED BY:

I. Cecil Felkner, Ph.D.
Program Manager
Dynamac Corporation

Signature: I. Cecil Felkner

Date: 2-6-85

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1. CHEMICAL: EPTC

2. TEST MATERIAL: Eptam Tech 97.8%; Lot No. 8799205; described as a yellow liquid; active ingredient S-ethyl dipropylthiocarbamate.

3. STUDY/ACTION TYPE: Teratogenicity Study in Mice.

4. STUDY IDENTIFICATION: Beliles, R. P. and Scott, W. J. Eptam-safety evaluation of teratological study in the mouse. (Unpublished Study No. T-6529 prepared by Woodard Research Corporation, Herndon, VA for Stauffer Chemical Company; dated April 6, 1967. Accession No. 247780.)

5. REVIEWED BY:

James R. Plautz, M.S.
Principal Author
Dynamac Corporation

Signature: James R. Plautz
Date: February 6, 1985

Ronald D. Hood, Ph.D.
Independent Reviewer
Dynamac Corporation

Signature: Lucil Feltner -for-
Date: 2-6-85

6. APPROVED BY:

Guillermo Millicovsky, Ph.D.
Technical Quality Control
Dynamac Corporation

Signature: G Millicovsky
Date: 6 Feb 85

Chad Sandusky, Ph.D.
EPA Scientist

Signature: Chad B Sandusky
Date: 2-6-85

Chris Chaisson, Ph.D.
EPA Section Head

Signature: C F Chaisson
Date: 2-6-85

7. CONCLUSIONS:

The potential teratogenic effects of the test material (administered by dietary inclusion at concentrations of 0, 53, and 160 ppm) in mice could not be evaluated on the basis of this study due to the following deficiencies:

a. Absence of maternal effects even at the highest level used in this study.

b. Utilization of only two groups dosed with Eptam consisting of 10 mated females (to be delivered by caesarean section) per group. The resulting number of pregnant animals C-sectioned were only 7, 8, and 6 for the 0, 53, and 160 ppm groups, respectively.

c. Homogeneity, stability and concentration of the test material in the feed was not presented.

d. Maternal food consumption data (which is essential in determining the actual intake of the test material) were not presented.

d. Absence of individual data for maternal clinical observations, fetal body weights, and external, visceral, and skeletal fetal examinations.

Due to the above listed deficiencies, this core study was considered to be invalid.