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DATA EVALUATION REPORT

Study Type: 83-5, Chronic Toxicity/Oncogenicity

TOX Chem No.: 893C
MRID No.: None

Accession Number: 402140-06 (Vol. 1-9)

Test Material: Sulfosate

Synonyms: SC-0224

Study Number: T-11813

Sponsor: Stauffer Chemical Company

Testing Facility: Stauffer Laboratory
Farmington, CT

Title of Report: Two-Year Chronic Toxicity and Oncogenicity Dietary Study with SC-0224 in Mice

Authors: Pavkov, K.L.; Turnier, J.C.

Report Issued: April 3, 1987

Conclusions: [Tentative]

The oncogenic potential was negative at the maximum tolerated dose (MTD) of 8000 ppm (highest dose tested [HDT]). The systemic NOEL is 1000 ppm. Body weight and food consumption were significantly decreased in 8000 ppm male and female mice during the study. There were no compound-related effects in palpable masses, hematology, clinical chemistry, and organ weights. Amyloidosis was frequent but not compound-related. In males at 8000 ppm there was an increased incidence of white matter degeneration in the lumbar region of the spinal cord. In female mice, epithelial hyperplasia of the duodenum occurred at an increased incidence at 8000 ppm.

Classification: Core-Supplementary, because the tissue masses listed in Table I (clinical observations) and Table L (necropsy observations) were not clearly identified in the histopathology observations (Table N) as being histologically examined. This deficiency has to be resolved.

II. Two-Year Chronic Toxicity and Oncogenicity Dietary Study With SC-0224 in Mice (Stauffer Labs Report No. T-11813; April 3, 1987).

Test Material--Technical SC-0224 (Trimethylsulfonium carboxymethylaminomethylphosphonate, active ingredient); Lot No. EHC 0586-08 (WRC Lot No. JHC-8865-20-1). Clear aqueous solution containing 56.17% active ingredient (w/w).

Experimental Design--Randomized groups of male and female Charles River (Kensington, NY) CD-1 mice (Crl:CD®-1(ICR)BR) were used in the study. The mice were identified by an ear tag and were housed individually.

The test material was administered continuously in the diet (Purina Certified Rodent Chow Meal 5002) for 22 months. The experimental design is shown below:

Dose Level	Number of Animals	
ppm ai	Male	Female
Control[a]	60	60
0[b]	80	80
100	80	80
1000	80	80
8000	80	80

[a] Basal diet without vehicle.
[b] Basal diet plus 1% propylene glycol vehicle.

There were interim sacrifices of variable numbers of mice at 6, 12, and 18 months. The number of mice scheduled for the full 22-month study duration was 50/sex/group.

Mice were observed twice daily for toxic signs. A general physical examination was performed on all test animals once per week including palpatation for nodules or tissue masses. Moribund mice were sacrificed to lessen the likelihood of unobserved death and subsequent tissue autolysis.

Individual body weights were recorded weekly for the first 13 weeks of the study and thereafter every other week. Body weights at the time of necropsy were recorded

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for animals sacrificed at 6, 12, or 18 months and at study termination. Individual food consumption was measured weekly during the first 13 weeks of the study and on alternate weeks thereafter by determining the sum of the allocated feed for a 7-day interval minus the residual from the 7-day period. Feed efficiency was calculated at each interval. Weight loss occasionally resulted in negative values for feed efficiency.

Blood samples were drawn for hematologic analyses (listed below) from 10 fasted animals of each sex in each dose group and vehicle control (0 ppm) at 6, 12, and 18 months and the 22-month termination (the control basal diet group was evaluated only at 12 and 22 months). The mice were anesthetized with sodium pentobarbital and the blood drawn from the abdominal aorta using an 18 to 21 gauge needle and a pediatric Butterfly® catheter prior to exsanguination. Hematology parameters evaluated included:

Hematocrit (Hct)
Hemoglobin (Hgb)
Erythrocyte count (RBC)
Total leukocyte count (WBC)
Differential leukocyte count (also prior to termination of any animal)
- Immature neutrophils (Bands)
- Mature neutrophils (Segs)
- Lymphocytes (Lymph)
- Monocytes (Mono)
- Basophils (Baso)
- Eosinophils (Eos)

Platelet count (PLT)
Prothrombin time (PT)
Partial thromboplastin time (PTT)

Samples for blood chemistry were obtained from 10 fasted mice/sex/dose group (same animals used for hematologic analyses) at 6, 12, 18, and 22 months. The blood chemistry parameters evaluated are listed below. When sample volume was insufficient, those parameters of the highest priority were measured in the following order:

Asparate aminotransferase (SGOT)
Alanine aminotransaminase (SGPT)
Alkaline phosphatase (Alk. Phos.)
Total protein (T. Prot.)
Albumin (Alb)
Blood urea nitrogen (BUN)
Glucose (Glu)
Total cholesterol (Choles)
Serum cholinesterase (S ChE)

Red blood cell cholinesterase (RBC ChE)
Total bilirubin (T Bili)
Creatinine (Creat)
Triglycerides (Triglyc)
Sodium (Na)
Calcium (Ca)
Potassium (K)
Chloride (Cl)
Gamma glutamyl transferase (GGT)
Inorganic phosphorus (Phos)
Creatinine phosphokinase (CPK)
Lactate dehydrogenase (LDH)

The right or left half of the brain from five mice/sex/dose level was homogenized at the 6-, 12-, 18-, and 22-month sacrifice to measure the cholinesterase activity. Activity was expressed per gram of protein (Lowry method for protein analysis) at 6 and 12 months and per gram of tissue at 18 and 22 months.

Urinalyses were performed for 10 fasted mice/sex/dose level (same animals mentioned above in hematology). The parameters evaluated included:

pH
Protein (Prot)
Glucose (Glu)
Ketones (Ket)
Occult blood (Occ Bl)
Urobilinogen (U-blin)

All mice were necropsied by trained prospectors under the direction of a veterinary pathologist. The animals were anesthetized by injecting saline-diluted sodium pentobarbital IP and exsanguinated by severing the abdominal aorta and vena cava. They were examined for external abnormalities, including palpable masses. Viscera and body cavities were also examined.

The following tissues were fixed in 10% neutral buffered formalin or 2.5% buffered glutaraldehyde:

*Heart
Ascending aorta
Thoracic aorta
Buccal/alveolar mucosa
Mandibular salivary gland
Parotid salivary gland
Tongue
Esophagus
Stomach
Eyes
Harderian glands
Auditory sebaceous glands
Middle ear(s)
Pituitary
Thyroid
Parathyroids
*Adrenals
Thymus
*Spleen

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Duodenum	Bone marrow/sternum
Jejunum	Mesenteric lymph node
Ileum	Mediastinal lymph node
Cecum	Skin and mammary gland
Colon	Skeletal muscle (thigh)
Rectum	Bone tibia/femur and joint sternum
Pancreas	
*Liver	*Kidneys
Gallbladder	Urinary bladder
*Brain	*Testes
Cervical spinal cord	Epididymides
Thoracic spinal cord	Prostate
Lumbar spinal cord	Seminal vesicles
Sciatic nerve	Coagulating glands
Nasal passage	*Ovaries
Paranasal sinus	Vagina
Nasopharnyx	Cervix
Larynx	*Uterus
Trachea	Gross lesions (specified by the pathologist)
*Lungs	

Those organs marked (*) above were weighed for mice sacrificed at the interim and final terminations. The paired organs were weighed separately. All tissues on the above list were routinely processed for light microscopic examination for all animals. Remaining wet tissue specimens were kept in fixative within gas-tight plastic bags and stored in the EHC archives.

Statistical Analysis

Continuous data were analyzed using a one-way analysis of variance (ANOVA; Winer, 1962) and Dunnett's Test (Dunnet, 1964) to compare test groups with controls. Test group data for hematology, clinical chemistry, and organ weights were compared to the 0 ppm (control) dose groups at 6 and 18 months and were compared to the basal diet (control) groups at 12 and 22 months. Quantal data, such as necropsy findings, clinical observations, and histopathologic findings were compared using Fisher's Exact Test (Siegel, 1956) with Bonferonni's correction (Ingelfinger, et al. 1983). The criterion for statistical significance was $p < 0.05$. Values of $p < 0.01$ were also indicated. The statistical significance was not determined at the $p < 0.001$ level because all Dunnetts' tables only include 0.05 and 0.01 values.

Results:

The average concentrations of SC-0224 active ingredient (measured by separate anion and cation analysis) were within 15 percent (anion analysis) and 20 percent (cation analysis) of the nominal values measured at regular intervals during the study.

Mean body weight values of male mice at 8000 ppm were significantly decreased during the study in comparison to controls. At study week 1, the mean body weight of control, 0, 100, 1000, and 8000 ppm male mice were 34, 33, 33, 33, and 32 g, respectively. At termination of the study in week 95, the body weight of male mice at control, 0, 100, 1000, and 8000 ppm were 44, 42, 45, 43, and 39 g, respectively. The mean body weight values of the 8000 ppm male mice were decreased by 3 to 11 percent during most of the study.

Similarly in female mice of the 8000 ppm group, the mean body weight values were decreased by 4 to 17 percent during most of the study. At study week 1, the mean body weight values of control, 0, 100, 1000, and 8000 ppm female mice were 25, 25, 26, 25, and 22 g, respectively. At termination of the study in week 95, the mean body weight values of female mice in the control, 0, 100, 1000, and 8000 ppm groups were 35, 35, 38, 35, and 29 g respectively. The significant decreases at 8000 ppm in male and female mean body weight values are considered sufficient evidence that an MTD dose was used in the study for both sexes.

Part of the decreased body weight values at 8000 ppm in both sexes were apparently due to decreased food consumption. The grand mean values (g/day) for food consumption for control, 0, 100, 1000, and 8000 ppm male mice were 4.8, 4.8, 4.8, 4.8, and 4.6, respectively. The decreased food consumption at 8000 ppm amounted to about 4 percent for male mice as determined by grand mean differences.

For female mice, there were similar decreases in grand mean food consumption values, amounting to an 8 percent decrease at 8000 ppm in comparison to controls. The grand mean values (g/day) for female mice at control, 0, 100, 1000, and 8000 ppm were 5.1, 5.0, 5.2, 4.9, and 4.7, respectively.

Compound intake for male mice (grand mean daily doses) were 11.7, 118, and 991 mg/kg/day for the 100, 1000, and 8000 ppm groups, respectively.

For female mice, the compound intake expressed as grand mean daily doses were 16.0, 159, and 1341 mg/kg/day for the 100, 1000, and 8000 ppm groups, respectively.

Grand mean values for feed efficiency for male mice through 22 months (20 months for 0 ppm group) were 0.8, 0.9, 0.9, 0.9, and 0.7 for control, 0, 100, 1000, and 8000, respectively. The grand mean values for feed efficiency for female mice through 22 months were 1.1, 1.0, 1.1, 1.0, and 0.7 for control, 0, 100, 1000, and 8000 ppm, respectively.

Survival of male mice was unaffected by treatment. Male mice of the 0 ppm group were sacrificed at week 89 when 12 (out of 50 at risk) had survived. The remaining groups of male mice were sacrificed at week 95 when survivors numbered 14, 21, 12, and 21 of the control, 100, 1000, and and 8000 ppm groups, respectively. At week 95, the surviving female mice numbered 17, 15, 14, 13, and 34 for the control, 0, 100, 1000, and 8000 ppm groups, respectively. Survival was apparently increased in 8000 ppm female mice in comparison to controls.

There were no compound-related toxic signs observed in male or female mice during the study.

The most frequent observations were abscesses, alopecia, chromodacryorrhea, chromorhinorrhea, conjunctivitis, dehydration, diarrhea, reduced activity, convulsions, distended abdomen, abrasions, hair loss, rough coat, scabs, and tremors.

There were no compound-related ophthalmoscopic findings at 6-, 12-, and 18-month interim examinations or at the 22-month terminal examination. The most frequent ocular observations were corneal opacity and cataracts.

There were no compound-related findings with respect to palpable masses for male and female mice.

Mean hematological values for male mice showed a statistically significant increase in hemoglobin of the 1000 ppm group at 18 months. This finding was not considered toxicologically significant since it was not dose related and control values (0 ppm) at 18 months were lower than control values at other intervals.

In female mice, the statistically significant increases at 18 months in hematocrit and hemoglobin of the 100 and 1000 ppm groups were not considered toxicologically significant since these findings were not dose-related

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and were within the normal range of control and 0 ppm values at other intervals.

Similarly, increased erythrocyte values at 100, 1000, and 8000 ppm in female mice at 18 months were not considered toxicologically significant since these values were within the range of control and 0 ppm values at other intervals. Additionally, in male and female mice at all sampling intervals, there were no significant differences in monocytes, lymphocytes, mature neutrophils, immature neutrophils, eosinophils and basophils.

There were several statistically significant different clinical chemistry parameters in treated groups as compared to the control values at various intervals.

At 22 months, mean SGOT values of females of the 1000 ppm group were increased in comparison to controls (0 ppm = 75 IU/L; 1000 ppm = 125 IU/L) but this was not considered toxicologically significant since it was not dose related. Additionally, individual values for SGOT in females of the 1000 ppm group at 22 months ranged from 53 to 217 IU/L in comparison to a range of 46 to 144 IU/L for 0 ppm and 40 to 87 for control groups.

SGPT values, which would also be expected to be increased if SGOT values were toxicologically significantly increased, were comparable between controls and treated males and females at each sampling interval. Therefore, the increased SGOT values were not indicative of organ toxicity.

Alkaline phosphatase values in 8000 ppm females at 6 and 18 months were increased in comparison to control values, but these were only small increases. At 6 months, mean SAP values were: 0 ppm = 37 IU/L; 8000 ppm = 66 IU/L. At 18 months, mean SAP values were: 0 ppm = 37 IU/L; 8000 ppm = 55 IU/L. These increases were not dose-related and did not occur at 22 months. Therefore, they were not indicative of systemic or organ toxicity.

Mean values of serum total protein were decreased at 6 and 18 months in 8000 ppm females and decreased at 22 months in 8000 ppm males. Most of the decreased values were within the range of control values for male and female mice. At 6 months, range in females: 0 ppm = 4.1 to 4.8 g/dl; 8000 ppm = 3.7 to 4.4 g/dl. At 18 months, range in females: 0 ppm = 3.1 to 4.8 g/dl; 8000 ppm = 3.1 to 4.2 g/dl. At 22 months, range in males; control = 4.5 to 6.8 g/dl; 0 ppm = 4.0 to 7.5 g/dl; 8000 ppm = 3.8 to 4.6 g/dl.

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Albumin values were decreased at 100 ppm females at 6 months and globulin values were decreased at 8000 ppm males at 18 months. The albumin decrease was not dose related. The decrease in globulin was not considered toxicologically significant since most individual values at 8000 ppm (range from 1.7 to 1.9 g/dl) were within 0 ppm range (1.8 to 3.1 g/dl).

The decreased differences in total protein, albumin, and globulin were not considered toxicologically significant. Small increases in BUN in females at 8000 ppm at 6 and 12 months were not considered toxicologically significant. Most values in 8000 ppm females at 6 months were 17 to 29 mg/dl with the exception of female animal 4158 which was 55 g/dl. These values were for the most part within the range of individual control values (13 to 21 mg/dl). At 12 months, the range of values for controls encompassed most individual values at 8000 ppm. In females, control range: 21 to 36 mg/dl; 0 ppm = 19 to 51 mg/dl; 8000 ppm = 36 to 74 mg/dl.

The decreases in serum glucose in 8000 ppm males at 6 months and 8000 ppm females at 18 months were not considered toxicologically significant. At 8000 ppm in males at 6 months, individual values were 54 to 98 mg/dl, as compared to the range of 77 to 113 mg/dl in 0 ppm males. These individual values are comparable. At 18 months in females, 0 ppm values ranged from 42 to 158 mg/dl as compared to 52 to 150 mg/dl at 8000 ppm. These individual values are comparable.

Differences in serum cholesterol and triglycerides were unaffected by treatment. Differences in serum sodium, calcium, potassium, phosphorus, chloride, gamma glutamyl transferase, creatinine phosphokinase, and lactic dehydrogenase were either not toxicologically significant or sufficient quantities were not available for analysis.

The increase in total bilirubin in 8000 ppm males at 12 months, decreases in 1000 ppm males at 18 months, and decreases in 8000 ppm males at 22 months were not dose-related and were not considered toxicologically significant.

The decreases in serum creatinine at 100 and 8000 ppm in males at 22 months and the increases in 100 and 1000 ppm in females at 22 months were not dose-related and were not considered toxicologically significant.

Therefore, in toto, clinical chemistry findings in male and female mice at each sampling interval did not reveal any compound-related or toxicologically significant differences.

Analysis of male and female brain, RBC, and serum cholinesterase activity did not reveal any toxicologically significant differences. Decreased mean values in brain cholinesterase in 100, 1000, and 8000 ppm female mice at 12 months were not dose-related. Similarly, the increased mean values of brain cholinesterase in 100 ppm females at 22 months were not dose-related and were not toxicologically significant. Most individual cholinesterase values in treated mice were within 25 percent of the control values and mean values were not dose related.

There were no compound-related effects in urinalysis values and findings.

At gross necropsy, the incidence of female mice exhibiting dehydration showed a dose-related increase (4, 9, 13, 18, and 19% in control, 0, 100, 1000, and 8000 ppm groups, respectively. There was also an increase in emaciation in female mice at 8000 ppm (9%) as compared to controls (3%).

In males at 8000 ppm, gross necropsy revealed an increased incidence of cysts in the kidney (9%) as compared to controls and other groups (2 to 4%). Microscopically, however, the incidence of renal cysts in the 8000 ppm males (24%) did not exceed the incidence in controls and other groups (22 to 33%).

There were no compound-related effects in absolute organ weight, organ weights relative to body weight, and organ weight relative to brain weight in male and female mice.

The statistically significant decreases in absolute heart, kidney, liver, spleen, and testes weights in males and absolute adrenal, brain, heart, kidney, liver, lungs, spleen, and uterus weights in females at 8000 ppm are considered due to decreased body weight of mice in these groups.

The increased relative brain weight of 8000 ppm male and female mice at all sampling intervals also appears to be due to the decreased body weight of these animals at these times. Similarly, the decreased organ to brain weight changes in male and female mice at 8000 ppm appears due to the diminished overall organ and body weights of these animals in comparison to controls.

The most frequent systemic non-neoplastic histologic lesion was amyloidosis. It occurred in both sexes and the most common grades of the lesion were moderate and severe. The occurrence of amyloidosis was not compound-related. The total numbers of male animals in which

amyloidosis was a major factor in the cause of death were 28, 26, 19, 30, and 18 for control, 0, 100, 1000, and 8000 ppm, respectively. The total numbers of female animals in which amyloidosis was a major factor in the cause of death were 22, 23, 22, 22, and 9 for control, 0, 100, 1000, and 8000 ppm, respectively.

There was slightly increased incidence of epithelial hyperplasia of the duodenum in male mice at 8000 ppm, which was not considered compound related since it was not statistically significant.

Duodenum (Males)

Dose (ppm)	Control	0	100	1000	8000
No. Examined	51	75	73	72	73
Epithelial hyperplasia	7	9	6	8	12
Percent response	14	12	8	11	16

The grade of each lesion was slight.

The incidence of myocardial degeneration in male mice was 58, 49, 39, 34, and 50 percent for control, 0, 100, 1000, and 8000 ppm, respectively. The most frequent grade of the lesion was slight.

Glomerulonephropathy in male mice occurred in incidences of 3, 6, 6, 4, and 9 percent for control, 0, 100, 1000, and 8000 ppm, respectively. The most frequent grade of the lesion was slight. The occurrence of glomerulonephropathy was not considered compound-related.

Degeneration of the sciatic nerve occurred at an increased incidence in treated male mice. This lesion was not considered compound-related; however, it was not dose-related, statistically significant, and the grade of the lesion was slight. The incidences of sciatic nerve degeneration were 9, 15, 19, 21, and 21 percent in the control, 0, 100, 1000, and 8000 ppm groups, respectively.

The occurrence of lymphangiectasia of the skin occurred at increased frequency in male mice at 1000 and 8000 ppm.

Skin (Males)

Dose (ppm)	Control	0	100	1000	8000
No. Examined	59	80	79	78	77
Lymphangiectasia	0	1	2	4	6
Percent response	0	1	3	5	8

The grade of moderate for the lesion occurred at an incidence of 1, 1, 1, and 5 for the 0, 100, 1000, and 8000 ppm males. Additionally, the grade of moderate/severe occurred in two instances at the 1000 ppm level. Although it seems to be "dose-related," there were no other indications in any parameter in the entire study suggesting the lymphatic vessel system might be a primary target organ for this chemical. If anything at all, it might be a secondary effect resulting from the very widespread and severe amyloidosis observed in the study. Amyloidosis apparently caused general stasis in the blood and lymphatic circulation and drainage systems. Under these conditions, it is not at all surprising that some dilatation of the lymphatic vessels was observed in some animals.

Also occurring in a compound-related manner at the 8000 ppm level in male mice was an increased incidence of white matter degeneration of the lumbar region of the spinal cord.

Spinal Cord - Lumbar (Males)

Dose (ppm)	Control	0	100	1000	8000
No. Examined	59	80	79	80	79
Nerve-root degeneration	5	6	5	7	11
Percent response	9	8	8	9	14
White matter degeneration	1	2	3	3	6
Percent response	2	3	4	4	8

The incidence of nerve root degeneration was not statistically significantly increased at 8000 ppm (14 vs. 8%, 9%; 0 ppm and control) and is not considered compound-related. The incidence of white matter degeneration is statistically significantly increased (greater than 2.5X of control and 2X of 0 ppm) at 8000 ppm and is considered compound-related. Additionally, there was one instance of moderate grade of this lesion at 8000 ppm with the remainder of the grades of the lesion being slight.

White matter degeneration of the thoracic region of the spinal cord occurred at a high incidence in both control and treated male mice. The incidences were 70, 60, 53, 67, and 66 percent in the control, 0, 100, 1000, and 8000 ppm groups, respectively. The grades of the lesion were comparable among control and treated animals.

In female mice, the only non-neoplastic lesion which was considered compound-related was the increased incidence of epithelial hyperplasia of the duodenum at 8000 ppm.

Duodenum (Females)

Dose (ppm)	Control	0	100	1000	8000
No. Examined	52	70	77	71	75
Epithelial hyperplasia	5	9	12	11	18
Percent response	10	13	16	15	24

All grades of the lesion were slight.

Other non-neoplastic lesions in female mice occurred at comparable incidences and grades between control and treated animals.

There were no compound-related neoplastic lesions in male and female mice. Additionally, there was no decrease in latency. The most frequent neoplasms observed in male and female mice were in the liver and lungs.

The incidences of the most commonly found tumors in males are shown below.

Liver (Males)

Dose (ppm)	Control	0	100	1000	8000
No. Examined	58	79	79	78	78
Hepatocellular Adenoma	7	8	6	4	2
(Percent)	12%	10%	8%	5%	3%
Hepatocellular Carcinoma	3	6	5	6	1
(Percent)	5%	8%	6%	8%	1%

Lungs (Males)

Dose (ppm)	Control	0	100	1000	8000
No. Examined	59	80	79	79	80
Adenoma	8	4	7	9	5
(Percent)	9%	5%	9%	11%	6%
Adeno-carcinoma	3	2	3	5	1
(Percent)	5%	3%	4%	6%	1%

In female mice, there were 3/80 hepatocellular adenomas only at the 8000 ppm level and there were no hepatocellular carcinomas. In the lungs of female mice, the following incidences of pulmonary adenomas and adenocarcinomas were observed.

Lungs (Females)

Dose (ppm)	Control	0	100	1000	8000
No. Examined	60	79	80	80	79
Adenoma	2	1	5	3	0
(Percent)	3%	2%	6%	4%	0%
Adeno-carcinoma	1	1	2	3	0
(Percent)	2%	2%	3%	4%	0%

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Discussion

Mean body weight values of male and female mice were significantly decreased at 8000 ppm during the study. In male mice, the decreases were 3 to 11 percent and in female mice, the decreases were 4 to 17 percent. Part of the decreases in body weight were due to decreases in food consumption in male and female mice at 8000 ppm.

The significant decreases in male and female body weight at 8000 ppm are considered evidence that an MTD for both sexes was used in the study.

Survival of male mice was unaffected by treatment. High-dose (8000 ppm) females survived better than controls. There were no compound-related effects in toxic signs, clinical observations, palpable masses, ophthamological findings, hematology, clinical chemistries, and organ weights.

The most frequent systemic non-neoplastic histologic lesion was amyloidosis. It occurred in both sexes and the most frequent grade was moderate/severe.

In male mice, the incidence of white matter degeneration was considered compound-related at 8000 ppm in the lumbar region of the spinal cord. 1.5= 600 mg/kg/day

In female mice, epithelial hyperplasia of the duodenum occurred at an increased incidence at 8000 ppm and was considered compound related. The systemic NOEL was 1000 ppm.

The oncogenic potential was negative for male and female mice. There was no decrease in latency.

However, these are tentative conclusions since the study is Core-Supplementary.

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16861:I/C:Dykstra:KENCO:12/15/87:DD:vo:dg:rw:
R:16892:Dykstra:KENCO:12/22/87:CB:VO:CB

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