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DATA EVALUATION REPORT

STUDY TYPE: 90-Day/Gavage/Dog/86-3114

Tox. Chem. No.: 753

ACCESSION No: 404604-02. MRID No.:

TEST MATERIAL: Sodium Chlorate.

SYNONYMS: $NaClO_3$.

STUDY NO.: 86-3114.

SPONSOR: Sodium Chlorate Task Force, Oklahoma City, Oklahoma.

TESTING FACILITY: Biodynamics, Inc., Mettlers Road, East Millstone, NJ 08873.

TITLE OF REPORT: A Subchronic (3 Month) Oral Toxicity Study In The Dog Via Gavage Administration of Sodium Chlorate.

AUTHORS: Debra S Barrett.

REPORT ISSUED: October 19, 1987.

CORE CLASSIFICATION: Supplementary, because additional information and data must be submitted.

CONCLUSIONS: The adrenal, and spleen weights, and organ/body weight ratios in males were increased at the HDT. Only the spleen weights in females were increased at the HDT. No effects were reported after histological examination of either organ. Hypercellularity of the bone marrow of males appeared to increase in severity and number of animals responding as the dose was increased. The effect was less pronounced in females. Increased brown pigment probably was seen in reticuloendothelial cells from the spleen and liver of males and females in the HDT. None of the effects were considered sufficiently adverse to establish an effect level. The NOEL is > 360 mg/kg/day(HDT).

Dose Levels administered by gavage: 0, 30, 60, and 360 mg/kg/day.

A. MATERIALS:

1. Test compound: Sodium chlorate, Description; white granular solid. Batch # None indicated, Purity 100%, Source: Kerr-McGee Chemicals Corp., Hamilton Mississippi 39746, contaminants: list in CBI appendix.



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2. Test animals: Species: Dogs, Strain: Beagle, Age:5.5 - 6.5 months old, Weight: Males 8.1(6.8-9.6) kg, Females 7.8(6.2-8.9)kg, Source: Marshall Farms USA, Inc., North Rose, NY 14516.
Acclimatization period was 4 weeks, temperature was 64-82° F, ratio of light:dark = 12:12, humidity was not specified.

B. STUDY DESIGN:

1. Animal Assignment - Animals were assigned randomly to 4 blocks such that the average weight of each block was uniform.

| Test group | | Dose in diet mg/kg/day | Main Study 3 months Male | Main Study 3 months Female | Clinical 6 wks & 13 wks Male | Clinical 6 wks & 13 wks Female | Sacrifice 3 months Male | Sacrifice 3 months Female |
|---|---|---|---|---|---|---|---|---|
| 1 | Cont. | 0 | 4 | 4 | 4 | 4 | 4 | 4 |
| 2 | Low (LDT) | 10 | 4 | 4 | 4 | 4 | 4 | 4 |
| 3 | Mid (MDT) | 60 | 4 | 4 | 4 | 4 | 4 | 4 |
| 4 | High(HDT) | 360 | 4 | 4 | 4 | 4 | 4 | 4 |

2. Stability Studies - Samples of solutions of sodium chlorate were stored at room temperature for 14 days of stability studies.

Results - All values were within 2.5% of nominal, indicating that sodium chlorate is stable in water at room temperature for at least 14 days.

3. Animals receive food (Purina Certified Canine Diet #5007) and water (Elizabethtown Water Co.) ad libitum.

4. Statistics - The following procedures were utilized in analyzing the numerical data: Equality of means - ANOVA. Equal variances - Bartlett's test. Differences between means - Dunnett's test. Nonparametric equality of means - Kruskal-Wallis test. Differences from control - Dunn's Rank Sum test. Other test used were standard regression techniques, and Jonckheere's test. The following were reported to be analyzed statistically: Body weights, food consumption, hematology, clinical chemistry parameters, terminal body weights, organs, and organ/body weight ratios.

5. Quality assurance statement was signed by Elizabeth Hay, Chairperson of the Sodium Chlorate Task Force, Debra S Barrett, Study director, and Florence S Gilson, Supervisor of Quality Assurance, on September 15, 1987.

C. METHODS AND RESULTS:

1. Observations - Animals were inspected at least twice daily for signs of toxicity and mortality.

Results - Toxicity - One male demonstrated excessive weight loss at the HDT. One male demonstrated yellow/brown watery stool, and yellow exudate in the eyes at the MDT. One female demonstrated

emesis during week 1, 2, and 3, and another 2 female dogs demonstrated yellow/brown watery stool at the HDT. One female dog demonstrated salivation and excitability, and another female dog demonstrated mucoidal stool at the MDT. One female dog demonstrated yellow/brown watery stool at the LDT.

Mortality (Survival) - No unscheduled mortality occurred.

2. Body Weight - They were weighed weekly from one week prior to initiation of the dosing, and then weekly for 13 weeks.

Results - The average body weights of males were nominally slightly increased or were equivalent to control body weights 13 of 13 weeks of the study. The average body weights of females were nominally, but only slightly, increased or equivalent to control body weights for 12 of the 13 weeks at the LDT and HDT and 7 of the 13 weeks of the study. The average body weight of females at the MDT was nominally increased or equivalent to controls.

The average body weight gain was nominally greater at the HDT in males (0.8 kg) and females (2.5 kg) than control weights (males, 0.4 and females, 2.0 kg, respectively). There appeared to be no dose related body weight gains or decrements among dosed males or females.

3. Food consumption - Consumption was reported only on a gram per kg body weight per day bases, and thus it is not readily readable as efficiency of food utilization. However, if evidence of excess food consumption per kg of body weight occurred, decreased efficiency could be suspected.

Results - Food consumption - In males at the MDT and HDT, the average food consumption per kg body weight was nominally increased compared with the control for 11 of the 13 weeks of the study. In males at the LDT, the average food consumption per kg body weight was nominally increased for 9 of the 13 weeks of the study. In females at the MDT and HDT, the average food consumption per kg body weight was nominally increased for 4 of the 13 weeks of the study. In females at the LDT, the average food consumption per kg body weight was nominally increased 6 of 13 weeks of the study.

Food efficiency - Can not be readily calculated from the data given, but from the patterns of body weight increase and food consumption per kg of body weight, there appears to be no evidence of decreased food efficiency.

Compound intake - Not applicable because the test compound was administered by gavage.

4. Ophthalmological examinations were performed pretest on an unknown number of animals. The number of animals subjected to ophthalmological examination were not specified.

Results - Retinal folds were seen in both eyes of one female dog, and nuclear Y lens opacities were seen in both eyes of a





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male dog during pretest examination. All animals studied demonstrated normal eyes at termination.

5. Blood was collected before treatment and at 6 weeks and at 3 months for hematological and clinical analysis from animals. The CHECKED (X) parameters were examined.

a. Hematology -

X Hematocrit (HCT)*
X Hemoglobin (HGB)*
X Leukocyte count (WBC)*
X Erythrocyte count (RBC)*
X Platelet count*
X Methemoglobin
Total plasma protein (TP)
X Leukocyte differential count
Mean corpuscular HGB (MCH)
Mean corpuscular HGB conc. (MCHC)
Mean corpuscular volume (MCV)

Results - HCT, HGB, and RBC was normal at 6 weeks and 13 weeks in males and females. Correspondingly platelet and leukocyte differential counts were all normal at week 6 and week 13 in males and females. Smears were made with potenial reticulocyte counts, but the data was not collected. Methemoglobin percent was about twice that of control values in the 13 week determination in males and females and in females at the HDT at the 6 week determination. This elevation was not statistically significant, and the numerical size of the value was similar to the variation seen in the pretest determinations and the standard deviation. Thus, the nominal increase seen may have been incidental.

b. Clinical Chemistry

Electrolytes:

X Calcium*
X Chloride*
Magnesium*
X Phosphorus*
X Potassium*
X Sodium*

Other:

X Albumin*
X Blood creatinine*
X Blood urea nitrogen*
Cholesterol*
Globulins
X Glucose*
X Total bilirubin*
X Total protein*
Triglycerides (TG)

ENZYMES:

Alkaline Phosphatase (AP)
Cholinesterase (CHE)
Creatinine phosphokinase* (CP)
Lactic acid dehydrogenase (LDH)
X Serum alanine aminotransferase (also SGPT)
X Serum aspartate aminotransferase (also SGOT)

Results - Clinical chemistry values generally did not differ from control values by more than a standard deviation at any dose level, and only in females at the 13 week determination, did the sodium level at the MDT and the potassium at the HDT become statistically significantly different from control values. None of the values at any dose level in males or females were considered to be biologically significant.

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6. Urinalysis - Not conducted.

7. Sacrifice and Pathology -
All animals that died and that were sacrificed on schedule were subject to gross pathological examination. The (X) tissues were collected for histological examination. The (XX) organs, in addition, were weighed.

| | | |
|---|---|---|
| X DIGESTIVE SYSTEM | X CARDIVASC./HEMAT. | X NEUROLOGIC |
| X Tongue | X Aorta* | XX Brain* |
| X Salivary glands* | X Heart* | X Periph nerve* |
| X Esophagus* | X Bone marrow* | X Spinal cord (3 levels) |
| X Stomach* | X Lymph nodes* | X Pituitary* |
| X Duodenum* | XX Spleen* | X Eyes(optic nerve) |
| X Jejunum* | X Thymus* | GLANDULAR |
| X Ileum* | UROGENITAL | XX Adrenal* |
| X Cecum* | XX Kidneys* | Lacrimal gland* |
| X Colon* | X Urinary bladder* | X Mammary gland* |
| X Rectum* | XX Testes* | X Parathyroids* |
| XX Liver* | XX Epididymides* | X Thyroids* |
| X Gall bladder* | X Prostate | OTHER |
| X Pancreas* | Seminal Vesicle | X Bone* |
| RESPIRATORY | XX Ovaries | X Skeletal musc.* |
| X Trachea* | X Uterus* | X All gross lesions & masses. |
| X Lungs* | | |

Results -

a. Organ weights - Organ weights and organ/body weight ratios of the brain, kidney, liver, and ovaries/testes/epididymides were comparable to control values at all dose levels in males and females. Absolute adrenal and spleen weights in males at the HDT were 150% and 167%, respectively, of control values. These organ/body weight ratios in the same group were 140% and 160%, respectively, of control values. The absolute spleen weights in females at the HDT were 165% of control values, and spleen/body weight ratios were 166% of control values. The adrenal weights in females at the HDT were comparable with control values.

b. Gross pathology - A nodule/mass was seen in the lung of one mid dose female, and one lung discoloration and emphysema were noted at the LDT and in a control animal, respectively. An irregular spleen surface was seen in one mid dose male and female, and one discolored spleen in a control female and in a low dose female. An enlarged and discolored epididymis was seen unilaterally in a male at the HDT. All of these gross findings were considered to be incidental and not related to the test chemical administration.

c. Microscopic pathology - See Table 1.

1) Non-neoplastic - A dose related minimal to slight multifocal inflammatory response may have been seen in the trachea of females(not shown). Various forms inflammatory responses were seen in the lungs of males and females of all groups with no apparent dose response relationship. The responses were graded minimal to slight with no apparent difference in severity among the groups. Spleens of all males and females demonstrated reticuloendothelial cell brown pigment. The grade of severity among almost all males and females in controls, LDT, and MDT was 1 for minimal, but the grade was 2 for slight among all males and females at the HDT. The pathology grade index was about double for the HDT groups(Table 1) over the control, LDT, and MDT. A similar finding of increased brown pigment occurred in the reticuloendothelial cells of the liver in males and females at the HDT. A slight increase in hypercellularity of the bone marrow of the sternum and femur at the HDT in males and females also may have occurred, but this finding was less obvious. One male dog demonstrated slight unilateral spermatic granuloma(s) and moderately severe unilateral oligospermia of the epididymis at the HDT, a finding which is probably incidental to treatment. No other possible treatment related histopathology was noted.

Specimens of the mammary tissue were missing from 7 females, 3 from the HDT.

2) Neoplastic - No neoplastic lesions were reported.

D. DISCUSSION:

The dose levels used in this study were too low to detect unequivocal toxicity. At higher dose levels in a range-finding study, emesis occurred, and it was stated that emesis would have prevented a study at higher dose levels. Emesis was reported to have occurred in the current study in one HDT female dog during week 1, 2, and 3. Also at the HDT 2 other females dogs developed yellow/brown watery stool, which may have been treatment related. Only one MDT male and one LDT female developed this diarrhea, and no other animals demonstrated vomiting.

Animal weights and food consumption were nominally elevated in the higher dose groups, but neither effect appeared to be treatment related.

No biologically significant hematological or clinical chemistry findings were reported.

The adrenal and spleen weights and their organ/body weight ratios of males at the HDT were increased. Only the spleen weight and spleen/body weight ratio of females were increased at the HDT. No histopathology was reported in either organ.

Various kinds of inflammatory responses in the lung, liver, and kidneys were the most frequent findings in all groups. These did not appear to be related to treatment. The severity of brown pigment in the reticuloendothelial cells of spleen and liver (Table 1) appeared to be approximately doubled at the HDT over that seen in controls and lower dose groups. However, no evidence of anemia was seen from the hematological determinations either at 6 or 13 weeks. Reticulocyte counts were not determined. (It should be noted that evidence of slight

anemia and an increase in reticulocyte were seen in rats dosed at 1000 mg/kg/day.) The increase in brown pigment seen at histological examination may be related to the nominally slight increase in methemoglobin formation which appeared to occur at the HDT, and to the increased spleen weights seen in the same group. There also appeared to be a dose related increase in hypercellularity of the bone marrow, especially in males, and possibly in females.

The pathologist discounted all these effects, indicating that all the histological findings were incidental and not related to treatment.

NOEL: > 360 mg/kg/day(HDT).
LEL: > 360 mg/kg/day(HDT).

* Recommended by Subdivision F (Oct. 1982) guidelines for chronic studies.

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Table 1.

Incidence and Severity of Selected Microscopic Pathology.

| Finding | Sex Group | Males 1 | Males 2 | Males 3 | Males 4 | Females 1 | Females 2 | Females 3 | Females 4 |
|---|---|---|---|---|---|---|---|---|---|
| **LUNGS** | | | | | | | | | |
| Perivascular lymphoid infiltrate | (A)[1] | 3 | 2 | 4 | 3 | 4 | 4 | 4 | 4 |
| | (B)[2] | 3 | 2 | 5 | 5 | 6 | 5 | 7 | 4 |
| **NODES** | | | | | | | | | |
| Mediastinal Reticuloendothelial cell, brown pigment | (A) | 2 | 3 | 2 | 1 | 1 | 2 | 2 | 1 |
| | (B) | 2 | 3 | 2 | 1 | 1 | 2 | 2 | 1 |
| **SPLEEN** | | | | | | | | | |
| Reticuloendothelial cell, brown pigment | (A) | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| | (B) | 4 | 5 | 4 | 8 | 4 | 4 | 4 | 8 |
| **MARROW, STERNUM** | | | | | | | | | |
| Hypercellularity | (A) | 1 | 2 | 3 | 3 | 2 | 0 | 4 | 4 |
| | (B) | 1 | 2 | 3 | 6 | 2 | 0 | 4 | 4 |
| **MARROW, FEMUR** | | | | | | | | | |
| Hypercellularity | (A) | 1 | 1 | 2 | 4 | 1 | 0 | 2 | 2 |
| | (B) | 1 | 1 | 2 | 7 | 2 | 0 | 2 | 4 |
| **LIVER** | | | | | | | | | |
| Microgranuloma | (A) | 4 | 2 | 3 | 3 | 4 | 3 | 3 | 4 |
| | (B) | 4 | 2 | 3 | 3 | 3 | 4 | 3 | 4 |
| Reticuloendothelial cell, brown pigment. | (A) | 3 | 2 | 4 | 4 | 4 | 4 | 4 | 4 |
| | (B) | 3 | 2 | 3 | 4 | 4 | 4 | 4 | 8 |
| **KIDNEY** | | | | | | | | | |
| Lymphoid cell infiltrate | (A) | 1 | 2 | 3 | 0 | 1 | 1 | 0 | 0 |
| | (B) | 1 | 2 | 3 | 0 | 1 | 2 | 0 | 0 |
| Proximal convoluted tubules, cytoplasmic vacuolation | (A) | 0 | 0 | 3 | 2 | 4 | 4 | 4 | 4 |
| | (B) | 0 | 0 | 3 | 2 | 4 | 4 | 5 | 6 |

[1] (A) = Number of animals responding.
[2] (B) = Pathology grade index = Sum of the product of: [Number of animals responding][Pathology grade of the lesion in the tissue of the animal]. To obtain the average pathological grade divide the Pathology grade index by number of animals responding, i.e. B/A.
Pathology grade: 1 - Minimal or very slight degree or amount present. 2 - Slight degree or amount present. 3 - Moderate degree or amount present. 4 - Moderately severe degree or amount present. 5 - Severe degree or large amount present.

INFORMATION AND DATA WHICH MUST BE SUBMITTED:

1) Seven of the 16 possible specimens of mammary tissue in females were missing at histological examination including 3/4 of the HDT. The results of histological examination of these missing tissues must be submitted.
2) The number of animals examined ophthalmologically must be stated.