US EPA ARCHIVE DOCUMENT

Reviewed by: David G Anderson, PhD. David G Anderson 5/10/88
Section VII, Tox. Branch (TS-769C).
Secondary reviewer: Albin B Kocialski, PhD. ABK 5/12/88
Section VII, Tox. Branch (TS-769C).

006717

DATA EVALUATION REPORT

STUDY TYPE: 90-Day Gavage/Rat/86-3112.

TOX. CHEM. No.: 753

ACCESSION No: 404448-01. MRID No.:

TEST MATERIAL: Sodium Chlorate.

SYNONYMS: $NaClO_3$.

STUDY NO.: 86-3112.

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 Of Sodium Chlorate In The Rat Via Gavage.

AUTHORS: Debra S Barrett.

REPORT ISSUED: December 4, 1987.

CORE CLASSIFICATION: Minimum.

CONCLUSIONS:

At the HDT of 1000 mg/kg/day, hemoglobin concentration, hematocrit, red blood cell counts were statistically significantly decreased, and reticulocyte count was statistically significantly increased in females. In males, only the hematocrit was statistically significantly decreased at the HDT. The adrenal weight was depressed in both males and females at the HDT. Histological lesions were detected in all groups with no apparent dose relationship.

Decreased body weight gain was demonstrated for females in all dosed groups, which was probaly related to an abnormally large body weight gain for control females. The efficiency of food utilization was slightly depressed, but within experimental error for all treated groups of females. The body weights of males were nominally lower in the two highect dose groups, but the values were not statistically significant.

The LEL was considered to be 1000 mg/kg/day and NOEL was considered to be 100mg/kg/day.

DOSE LEVELS ADMINISTERED: 0, 10, 100, 1000 mg/kg/day.

A. Materials:

1. Test Compound: Sodium chlorate, Purity 100%. Source: Kerr-McGee Chemical Corp., Hamiton, MS 39746. The contaminants listed in the CBI Appendix.

2. Test Animals: Rats. Species: Charles River CD-1 rats, from Charles River Breeding Laboratories, Kingston, NY. Age: At initiation of treatment 42 days. Weight: Males 205 g, females 143 g. Acclimatization, 14 days. Humidity was 23% - 86%. The temperature was 68 - 75 degrees F. The ratio of light:dark = 12:12.

B. Study Design:

1. Animal assignment
Animals were assigned randomly such that body weights were uniform among the groups. Animals were assigned to the following groups:

Test Group	Dose in diet (mg/kg/day)	Main Study 3 months M	Main Study 3 months F	Clinical chemistry M	Clinical chemistry F	Necropsy M	Necropsy F	Histo. M	Histo. F
1 Cont.	0	15	15	10	10	15	15	10	10
2 Low (LDT)	10	15	15	10	10	15	15	-	-
3 Mid (MDT)	100	15	15	10	10	15	15	-	-
4 High(HDT)	1000	15	15	10	10	15	15	10	10

M = Males; F = Females.

2. Diet preparation - Not applicable.

3. Administration - Test material was administered by gavage in 5 ml/kg/dose. The vehicle was distilled water.

4. Food and Water Administration - Ad libitum. Food was Purina Certified Rodent Chow # 5002. Water was from the Elizabethtown Water Company.

5. Statistics - The following procedures were utilized in analyzing the numerical data: Bartlett's Test for equal variances, Parametric ANOVA for differences among means, differences from controls, Dunnnett's, Krushal-Wallis (non-parametric), ordered response to dosage, Jonkheere's test, significantly different from control, Dunn's Rank Sum Test.

6. Quality assurance statement was signed by Elizabeth Hay, Chairperson, Sodium Chlorate Task Force, Debra S Barrett, Study Director, and on 12/2/87 by Florence S Gilson, Supervisor of Quality Assurance at Biodynamics.

C. METHODS AND RESULTS:

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

Results - Toxicity - Observations of dose related toxicity were reported not have occurred.

Mortality (Survival) - One spontaneous death occurred in a male in the MDT, and in one female in the HDT on day 69 and day 30, respectively. Both animals exhibited inferior body weight, but ante-mortem physical examination did not indicate a dose related cause of death.

2. Body Weight - They were weighed twice pretest and weekly until terminal sacrifice. The animals were fasted prior to weighing at terminal sacrifice.

Results -

Body weight gain in males was least at the HDT and was 96% of controls(Table Appendix E). In females at the LDT and HDT, body weight gain was statistically significantly different from controls from week 3 to week 12, and was nominally lower than controls at the MDT. The weight gain by week 12 in females was 85%, 93%, and 84% of controls at the LDT, MDT, and HDT, respectively(Table Appendix E). Data on the study was reported only for 12 weeks, thus body weight gains for 13 weeks can not be reported. Body weight for week 12 and body weight gain by week 11 and week 12 of the study are presented in Table 1.

Table 1.

Body Weight at week 12 and Body Weight gain (Week 11 and Week 12) - Week 0 (g)

	Body Weight Week 12		Body Weight Gain Males		Body Weight Gain Females	
Group	Males	Females	Wk 11	Wk 12	Wk 11	Wk 12
Control	541.5	327.6	324.4	337.2	178.6	182.3
10 mg/kg/day	573.6	295.6*	352.0	367.3	153.1*	154.2*
100 mg/kg/day	539.7	311.3	325.4	335.2	168.3	170.0
1000 mg/kg/day	523.1	294.2*	310.1	318.6	149.6*	152.1*

* Statistically significantly lower than controls.

Historical control data was submitted on six 90-day gavage studies in the Charles River CD rat, and are presented in Table 2. These historical studies indicate that the average female body weight after 13 weeks is 274.9(248.3 - 299.9) g, with an average

weekly body weight gain of 8.6(6.4 - 10.0) g (Since data were given starting with week 1, the weekly body weight gain data were calculated using 12 weeks.). The body weight of control females after 12 weeks in the current study was 327.6 g with an average weekly body weight gain of 13 g, 119% and 151% over the average historical control body weight and average weekly body weight gain, respectvely. The body weight gain of concurrent controls was 176% of the average body weight gain of historical controls. However, the body weight of the dosed groups also were larger than the historical control data submitted(Table 3). The body weight gain of the treated groups in the current study was about 147% to 164% of the body weight gain in the historical control data.

Table 2.

Week		Study A	Study B	Study C	Study D	Study E	Study F	Average of 6 Studies
1	Mean	180.0	190.2	171.1	146.5	169.9	170.1	171.3
	S.D.	8.6	20.6	8.5	12.1	7.6	5.7	
	N	10	30	20	20	15	10	
2	Mean	198.9	208.0	189.6	163.5	188.1	191.4	189.8
	S.D.	8.3	25.7	12.3	14.6	7.3	7.0	
	N	10	29	20	20	15	10	
3	Mean	224.9	221.2	210.9	187.1	202.7	209.5	209.4
	S.D.	9.6	27.2	12.7	19.1	7.5	8.5	
	N	10	29	20	20	15	10	
4	Mean	237.1	236.1	223.0	198.0	217.2	227.0	223.1
	S.D.	13.1	29.9	16.2	20.3	11.2	11.5	
	N	10	28	20	20	15	10	
8	Mean	272.5	260.2	257.4	229.3	244.0	268.0	255.2
	S.D.	16.5	31.1	18.1	25.0	15.2	22.0	
	N	10	26	20	20	15	10	
13	Mean	292.9	266.6	279.6	248.3	266.0	288.9	274.9
	S.D.	18.8	34.3	16.4	26.7	18.2	37.7	
	N	10	8	8	20	15	10	
Average Weekly Gain		9.6	6.4	9.0	7.5	9.0	9.9	8.6

006717

Table 3.

Body Weight and Body Weight Gain of Current Data Compared to the Average Historical Data.

Group (mg/kg/day)	Body Weight: Current study	Body Weight: Percentage of av. historical[a]	Body Weight Gain: Current study	Body Weight Gain: Percent of av.historical[b]
Control	327.6	119	182.3	176
10	295.6*	108	154.2*	149
100	311.3	113	170.0	164
1000	294.2*	107	152.1*	147

[a] = [Body weight/274.9]*100.
[b] = [Body weight gain/103.6]*100.

3. Food consumption and compound intake - Consumption was determined for a 6 day period, weekly. Efficiency was not calculated, relative efficiency was calculated from the weekly food consumption and the weekly body weight gain data.

Results - Food consumption - Weekly food consumption during 11 weeks and 12 weeks of study are reported in Table 4.

Table 4.

Group mg/kg/day	0	10	100	1000
	Weekly Food consumption for Males(g)			
Week 1	145.7	149.9	148.7	148.4
2	149.7	152.1	150.4	148.7
3	154.9	163.9	161.5	156.5
4	172.7	173.7	173.0	171.1
5	169.7	158.4	144.7	154.4
6	167.9	178.3	175.0	172.7
7	170.5	178.8	176.5	168.4
8	168.3	180.5	172.1	168.9
9	171.1	180.5	172.9	168.7
10	160.5	181.5	176.5	167.1
11	168.2	179.4	172.0	164.0
12[a]	173.8	186.4	179.2	162.6
Total for 11 wks	1799	1877	1823	1789
Total for 12 wks	1973	2063	1998	1952

Table 4 is continued on the next page.

006717

(Table 4 cont.) Weekly Food Consumption for Females(g)

Week 1	113.9	110.4	108.9	106.8
2	116.2	111.1	113.4	108.0
3	123.3	121.8	123.2	116.5
4	136.7	130.5	124.9	123.9
5	132.8	125.1	125.9	122.0
6	133.3	121.8	126.9	124.4
7	131.7	120.4	128.1	122.6
8	127.7	121.3	120.9	119.2
9	125.5	121.1	124.5	118.9
10	124.6	125.9	125.3	114.9
11	127.6	123.9	129.0	119.4
12[a]	128.8	125.4	120.2	120.4
Total for 0-11 wks	1393	1333	1351	1297
Total for 0-12 wks	1522	1459	1471	1417

[a] = Food consumption during week 12 was multiplied by 2 to correct the data to a 6 day food consumption used for other weeks. Food consumption data was collected for only 3 days for week 12 instead of the 6 days for other weeks.

Relative Food efficiency - was nominally decreased in the MDT and HDT males, but was small, and within the error of the determinations(98% and 95% of controls at each of the MDT and HDT, respectively). The overall relative efficiency of food utilization in females for 12 weeks was 88% of controls at the 10 mg/kg/day dose level, 97% of controls at the 100 mg/kg/day dose level, and 89% of controls at the 1000 mg/kg/day dose level. All appeared to be close to experimental error. The overall relative efficiency of food utilization from week 0 to week 11 and week 12 is reported in Table 4.

Table 4.

Overall Relative Efficiency of Food Utilization, reported as [total average body weight gain (g) from week 0 to 11 or 12]/ [total average food consumption (g) from week 0 to 11 or 12].

Group		0	10	100	1000 mg/kg/day.
Males	11 wks	0.180	0.188	0.178	0.173
	12 wks	0.171	0.178	0.168	0.163
Females	11 wks	0.128	0.115	0.125	0.115
	12 wks	0.120	0.106	0.116	0.107

Compound intake - Not applicable, since dosing was by gavage.

4. Ophthalmological examinations were performed pretest and weekly thereafter on an unknown number of animals. The number of animals examined was not stated.

Results - Focal retinopathy occurred in two control male rats and in one male and female in HDT. None of the findings were considered treatment related.

5. Blood was collected before treatment and at 3 months for hematological and clinical analysis from 10 animals/group. 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
X Reticulocyte counts
Total plasma protein (TP)
X Leukocyte differential count
X Mean corpuscular HGB (MCH)
X Mean corpuscular HGB conc. (MCHC)
X Mean corpuscular volume (MCV)
X Erythrocyte morphology

Results - At the HDT, hemoglobin concentration (HGB), hematocrit (HCT), red blood cell count (RBC) were decreased in males and females. All these values were statistically significant for females, only the HCT was statistically significantly lower in males. The following values were reported to be normal and similar to controls: MCH, MCV, MCHC, and reticulocyte counts in males. In females of the HDT reticulocyte count were statistically significantly increased. Methemoglobin was not different from control values at any dose level in males or females.

The differential leukocyte counts revealed no differences from control values.

b. Clinical Chemistry

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

ENZYMES:
Alkaline Phosphatase (AP)
Cholinesterase (CHE)
Creatinine phosphokinase* (CP)

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

006717

Lactic acid dehydrogenase (LDH)
X Serum alanine aminotransferase (also SGPT)
X Serum aspartate aminotransferase (also SGOT)

Results - Chloride was statistically significantly lowered in males at the HDT. SGPT was statistically significantly lowered in females at the HDT. No other effects were noted. The effects on chloride and SGPT are considered incidental to the study.

6. Urinalysis - No urinalysis was 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.

DIGESTIVE SYSTEM	CARDIVASC./HEMAT.	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*	X Lacrimal gland*
X Colon*	Urinary bladder*	Mammary gland*
X Rectum*	XX Testes*	X Parathyroids*
XX Liver*	XX Epididymides*	X Thyroids*
Gall bladder*	X Prostate	OTHER
X Pancreas*	X 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 - The adrenal weights in males and females at the HDT were statistically significantly depressed at terminal sacrifice. The relative kidney and liver weights were statistically significantly elevated in females at the HDT, but the absolute organ weights were not. The adrenal weights may have been treatment related, but the relative kidney and liver weights were probably due to the lower body weight of females in this dose group.

b. Gross pathology - one quarter to third of the animals in all groups demonstrated discolored lungs, but there was no indication of a dose relationship.

c. Microscopic pathology -

1) Non-neoplastic

No dose related histopathology was detected during histological examination of the organs and tissues. The lungs demonstrated histological findings in all groups with moderate lymphocyte infiltration. Other findings were reported equally among treated groups and controls, and were not considered treatment related. Minimal to slight hyperplasia of the islet cells of the pancreas was noted in 6/10 animals from the control, but only in 0/10 animals in the HDT. Extramedullary hematopoiesis and reticuloendothelial cell pigmentation in all spleens examined in all groups precluded determination of any dose response relationship. Histological findings in the liver were equally frequent in all groups examined. Congestion and acute/subacute inflammation were the most frequent findings in the kidneys. The findings were equally distributed among controls and treated groups.

2) Neoplastic - No neoplastic lesions were reported.

D. DISCUSSION:

The decreased weight gain effects in females demonstrated by this study were not considered real nor biologically significant. However, the statistically significant decreased body weight gain seen in females at the LDT and HDT are difficult to assess, because of the relatively large body weight gain by the controls, and the apparent lack of statistically significant decreased body weight gain at the MDT.

Examination of historical data on the body weights of six 90-day gavage studies conducted at Biodynamics on Charles River CD rats indicate that the average body weight of control females following 13 weeks of study was 274.9(248.3 -299.9) g, with an average weekly body weight gain of 8.6(6.4 - 10.0) g. Comparison of the present study indicates that the body weights and body weight gains after 12 weeks, respectively, were 327.6 g and 13 g. The testing facility concluded that body weight gain of controls was excessive, and that this excessive weight gain was responsible for the statistical significance of the body weight decrement seen in the LDT and HDT females. In addition, they concluded that the lack of a dose response in the body weight

decrement indicated that the response was due to biological variability.

The lack of a dose response relationship among dosed groups dose from 10 to 1000 mg/kg/day would appear to indicate that the body weight gain decrement among dosed females was relate to unknown factors other than the test material. In addition, no body weight gain decrement occurred in the dog at the HDT of 360 mg/kg/day, or in rats in the teratogenicity study at the HDT of 1000 mg/kg/day. Thus the body weight gain decrement in females was probaly due to the large body weight gain of females control animals and not due to treatment of the test material.

In females the HCT, HGB, and RBC were statistically significantly lower, and the reticulocyte counts were statistically significantly higher than controls at the HDT. In males only the HCT was statistically significantly lower than controls at the HDT. These effects were considered test chemical related.

No biologically significant clinical chemistry data was reported.

The depression in adrenal weights in male and females at the HDT were not correlated with any dose related histopathology of the adrenals.

Histological lesions were noted in all groups studied in the lung, liver, kidneys, urinary bladder, spleen, pancreas, and lymph nodes, but no dose related effects were noted. In some cases the lesions were present in the organs from all the animals studied. However, these lesions did not increase in severity with dose, and thus, they were assumed not be dose related.

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

RIN-2906-01

Page _____ is not included in this copy.

Pages 11 through 14 are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

✓ FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.
