CASWELL FILE

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

MAY 11 1992

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Monosodium Acid Methanearsonate (Methanearsonic Acid) - Developmental Toxicity Study in Rats (§83-3A)

Caswell No.: 582 MRID No.: 419264-01
HED Project No.: 1-1990 Chemical No.: 013803
Identification No.: 013803-042519

FROM: Alan C. Levy, Ph.D., Toxicologist Alan C. Levy 4-30-92
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Health Effects Division (H7509C)

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THRU: Elizabeth A. Doyle, Ph.D., Section Head E.A. Doyle 5/5/92
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and

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REQUEST: Review a Developmental Toxicity study in rats with Methanearsonic acid (Monosodium acid Methanearsonate)

CONCLUSIONS:

Methanearsonic acid was administered by gavage to pregnant rats at doses of 0, 10, 100 and 500 mg/kg on gestation days 6 through 15. The results were as follows:

10 mg/kg - maternal = none
fetal = none

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100 mg/kg - maternal = slight decrease in body weight gain and food consumption during the dosing period
fetal = none

500 mg/kg - maternal = a decrease in body weight gain and food consumption during dosing; anogenital staining and/or soft stools
fetal = lower group mean fetal body weights

Maternal No Observed Effect Level (NOEL) = 10 mg/kg
Maternal Lowest Observed Effect Level (LOEL) = 100 mg/kg - slight decrease in body weight gain and food consumption during dosing

Developmental No Observed Effect Level (NOEL) = 100 mg/kg
Developmental Lowest Observed Effect Level (LOEL) = 500 mg/kg - lower group mean fetal body weights.

The test article did not appear to cause any teratogenic effects.

Classification: Core Minimum

This study satisfies the Guideline requirements (§83-3A) for a developmental toxicity study in rats.

Reviewed by: Alan C. Levy, Ph.D. Alan C. Levy 4-30-92
Section IV, Tox. Branch II (H7509C)

Secondary reviewer: Elizabeth A. Doyle, Ph.D. E.A. Doyle 5/5/9
Section IV, Tox. Branch II (H7509C)

DATA EVALUATION REPORT

STUDY TYPE: Developmental Toxicity - Rat (§83-3A)

TEST MATERIAL: Methanearsonic acid (monosodium acid methanearsonate)

SYNONYMS: T-168-2, MAA, SDS-37161

Tox. Chemical No.: 582 **MRID No.:** 419264-01
HED Project No.: 1-1990 **Identification No.:** 013803-042519
Chemical No.: 013803

STUDY NUMBERS: Sponsor (Fermenta) = 89-0130
Performing Laboratory (Bio/dynamics) = 89-3456
Test Substance Analysis Laboratory (Ricerca) = 89-0130
Ricerca Document No.: 3190-89-0130-TX-000, 001,002 TS-001

SPONSOR: Fermenta ASC Corporation, Mentor, OH

TESTING FACILITY: Animal Study = Bio/dynamics Inc., East Millstone, NJ
Test Substance Analysis = Ricerca, Inc., Painesville, OH

TITLE OF REPORT: A Teratology Study in Rats with Methanearsonic Acid

AUTHORS: Bio/dynamics = Raymond E. Schroeder
Ricerca = M. Mizens and J. C. Killeen

REPORT ISSUED: Bio/dynamics = January 24, 1990
Ricerca = September 7, 1990

CONCLUSIONS:

Methanearsonic acid was administered by gavage to pregnant rats at doses of 0, 10, 100 and 500 mg/kg on gestation days 6 through 15. The results were as follows:

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500 mg/kg - maternal = a decrease in body weight gain and food consumption during dosing; anogenital staining and/or soft stools
fetal = lower group mean fetal body weights

Maternal No Observed Effect Level (NOEL, = 10 mg/kg
Maternal Lowest Observed Effect Level (LOEL) = 100 mg/kg - slight decrease in body weight gain and food consumption during dosing

Developmental No Observed Effect Level (NOEL) = 100 mg/kg
Developmental Lowest Observed Effect Level (LOEL) = 500 mg/kg - lower group mean fetal body weights

Classification: **Core Minimum**

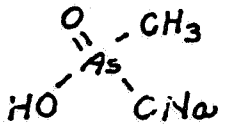
This study satisfies the Guideline requirements (§83-3A) for a developmental toxicity study in rats.

I. MATERIALS, METHODS AND RESULTS

A. Test Article Description

Name: Methanearsonic acid (monosodium acid methanearsonate, T-168-2, methylarsonic acid, MAA, SDS-37161)

Formula:



Lot Number: 107/84 (Batch No.)
Purity: 99.73% (>98% Ricerca Report)
Appearance: white powder
Storage: room temperature, in the dark

Vehicle: deionized water

B. Stability of Test Article

Analyses were peformed by Ricerca, Inc. This Ricerca Report indicates that the purity was ">98% SDS-37161 (recrystallized)" (Ricerca Report page 9, Report page 457). Table 1 presents purity and stability data.

Table 1

A SUMMARY OF PURITY/STABILITY ANALYTICAL DATA OF METHANEARSONIC ACID IN DOSING SOLUTIONS FOR A RAT DEVELOPMENTAL TOXICITY STUDY

	Assay No.	1.0 mg/ml	10.0 mg/ml	50.0 mg/ml
Day 0	1	0.9	-	52.0
	2	1.0	-	51.9
Day 15	1	1.0	-	49.4
	2	1.0	-	49.6
Mix	1	1.0	10.1	48.0
	1	1.0	9.9	49.6
	2	1.0	10.0	50.4
	2	1.0	10.0	50.2
	3	1.0	9.9	49.1
	3	1.0	9.8	49.6

NOTE: control assays = <0.01 mg/ml
Data extracted from Ricerca Report Tables 2-4, pages 15-17 (These are Report pages 463-465). Report pages 450-490 contain the complete Ricerca Assay Report.

Purity and stability assay data indicate that these are acceptable.

C. Dosing

Methanearsonic acid was administered by gavage in volumes of 10 ml/kg body weight/day on gestation days 6 through 15 at doses of 0 (deionized water), 10, 100 and 500 mg/kg/day. The vehicle was deionized water. Volumes were adjusted based on the most recent body weights. Fresh dosing solutions were prepared once before the initiation of dosing and 3 times during the dosing period. Because mating (day 0 of gestation) took place on 12 separate days, the 10 doses (gestation days 6-15) were administered to all rats in the study over a staggered period of 32 days.

D. Animals

CD® (Sprague-Dawley) rats were obtained from Charles River Laboratories, Inc., Portage, MI. At the initiation of mating, males (proven breeders) were about 23 weeks old and females were non-pregnant/nulliparous, about 10 weeks old, and had been acclimated for 23 days.

Animals were individually housed in stainless steel wire mesh suspended cages except during mating when one male was caged overnight with one female. Food and water were available ad libitum. Actual room temperature during the study was 72°F (68-82°F, out of desired range of 67-73°F 11 times). Actual room humidity during the study was 62% (50-77%, out of desired range of 30-70% on one occasion). There was a 12 hour light/dark cycle.

Animals were examined by a veterinarian before being assigned to the study. Mated females were placed in groups daily so as to keep the group mean body weights equal.

E. Mating

After a 1:1 overnight mating, vaginal smears were obtained and mating was considered to have taken place if sperm and/or a vaginal plug was observed. Day 0 of gestation was the day evidence of mating was noted. There were 25 females mated/group.

F. Observations

1. Physical

Mated females were observed A.M. and P.M. for

appearance, behavior, signs of toxicity, moribundity and mortality. Each was also given a detailed physical examination on gestation days 0, 6-15 and 20.

The only death was a 500 mg/kg rat (No. 4586) which died on gestation day 11 after having received 6 doses. The female was not pregnant and there did not appear to be an intubation injury. There was staining of the skin/fur in the ano-genital region on gestation day 10 and there was a loss of 63 g of body weight during days 6-11.

There were no clinical signs attributed to test article administration in the 10 or 100 mg/kg groups. At 500 mg/kg, 3 rats had ano-genital skin/fur staining at one or more intervals during treatment. Five rats from this group (including 1/3 with staining) were noted to have soft stools at one or more intervals during treatment or post-treatment. As neither the staining nor soft stools were reported in the controls, 10 or 100 mg/kg animals, the Report stated that this "low incidence" of stains and/or soft stools was, "... suggestive of a treatment related response."

2. Body Weights

Weights were recorded once during the acclimation period as well as on gestation days 0, 6, 9, 12, 16 and 20. Body weights and weight gains are presented in Table 2.

There was not a statistically significant nor a strong indication of a biologically significant difference in group mean body weights at any weighing interval regarding any of the groups. Also, group mean corrected body weights (final weight minus gravid uterine weight) appeared to be similar for all groups.

For body weight gains, the 10 mg/kg group means were similar to controls for all time periods. At 100 mg/kg, there was a lower gain ($p<0.01$ or 0.05) for the 12-16 and 6-16 day periods.

At 500 mg/kg, there was a slight numerical group mean loss (3 g) for days 6-9 (beginning of dosing) compared with gains of 9-10 g for the other 3 groups ($p<0.01$ versus control). During days 9-12, this high dose group mean weight gain was 20 g compared with 16, 12 and 13 for the 0, 10 and 100 mg/kg values. All 4 groups had similar mean gains for days 16-20 (61-67 g). For the entire dosing period (days 6-16), there was a lower group mean gain ($p<0.01$) at 500 mg/kg (31 g) compared with the control gain (52 g).

Methanearsonic acid at 500 mg/kg appears to have had an effect on body weight gain during the period of dosing with an overall gain during pregnancy (days 0-20) 11% less than the control group (146 versus 130 g). The two lower dose groups gained 136 g. The statistically significant lower gain at 100 mg/kg during days 12-16 and 6-16 is suggestive of a test article effect.

Table 2

GROUP MEAN BODY WEIGHTS AND WEIGHT GAINS DURING GESTATION IN A RAT TERATOLOGY STUDY WITH METHANEARSONIC ACID

Day mg/kg =	0	10	100	500
BODY WEIGHT (G)				
0	229	227	225	230
6	258	257	255	262
9	268	266	265	258
12	284	278	278	278
16	310	302	298	293
20	375	363	361	360
CORRECTED BODY WEIGHT (day 20 weight minus gravid uterine weight)				
Body Weight (g)	295	287	286	286
Uterine Weight (g)	80	76	75	74
BODY WEIGHT GAIN (g)				
0-6	29	30	30	32
6-9	10	9	10	-3**
9-12	16	12	13	20
12-16	26	24	20**	15**
16-20	64	61	63	67
6-16	52	45	43*	31**
0-20	146	136	136	130

NOTE: The number of pregnant females/group was (mg/kg) : 0 = 23, 10 = 25, 100 = 24 and 500 = 23. Data from one 100 mg/kg female were excluded due to incorrect body weight recording which resulted in an over-dose on gestation days 9-11.
Statistical Significance: * = $p<0.05$; ** = $p<0.01$
Data extracted or calculated from Report Appendices C, D and E, pages 105, 110 and 116.

3. Food Consumption

Data for this parameter were recorded for the following periods (days): 0-6, 6-9, 9-12, 12-16 and 16-20.

No adverse effect was noted for animals receiving 10 mg/kg.

Group mean food consumption (g/kg/day and g/rat/day) was less than the control value for one or more intervals during dosing at 100 and 500 mg/kg. This appears to be consistent with the body weight gain values. At 500 mg/kg, the days 16-20 value (g/rat/day) was essentially equal to the control (29 versus 28 g).

G. Reproductive Data

Complete postmortem examinations were performed on all mated females. Tissues with lesions were preserved.

The animals were sacrificed by exsanguination under ether anesthesia on gestation day 20. The intact uterus (ovaries attached) was weighed and the number and location of the following recorded for each uterine horn: live fetuses, dead fetuses, late resorptions, early resorptions and implantation sites. If no implants were observed, the uterus was stained with ammonium sulfide. The animal was considered non-pregnant if no post-staining implants were observed. The ovaries were examined for the number of corpora lutea.

Table 3 presents a summary of the reproductive data.

Table 3

A SUMMARY OF REPRODUCTIVE DATA FROM A RAT DEVELOPMENTAL TOXICITY STUDY WITH METHANEARSONIC ACID

Parameter mg/kg =	0	10	100	500
Females Mated - No.	25	25	25	25
Pregnant - No.	23	25	24a	23
Litters with Viable Fetuses - No.	23	25	24	23
Female Mortality - No.	0	0	0	1
Corpora Lutea - group mean	16.2	15.9	16.0	16.3
Implantation Sites - group mean ..	15.3	15.3	14.8	15.3
Viable Fetuses - mean litter size	14.4	14.3	14.0	14.7
Dead Fetuses	0	0	0	0
Resorptions - total	19	24	20	12
Litters with Resorptions	12	14	12	10
Fetal Body Weight - group mean ...	3.4	3.3	3.3	3.1**
Males	3.5	3.4	3.4	3.2**
Females	3.3	3.2	3.2	3.0**

a = One of 25 excluded due to incorrect weighing which resulted in overdosing
Statistical Significance: * = $p<0.05$; ** = $p<0.01$
Data extracted from Report Appendix G, page 131.

Two control and two 500 mg/kg females were not pregnant. There was no apparent test article effect on any of the uterine or ovarian parameters examined.

Male, female and combined sex fetal weight data indicated that, at 500 mg/kg only, there was a statistically significant ($p<0.01$) group mean lower weight when compared with control data. Therefore, this dose appeared to have a fetotoxic effect.

H. Fetal Evaluations

1. External/Visceral/Head

Each fetus was subjected to the following: gross examination for external changes, weighing and sexing.

About half of the fetuses in each litter (alternating within a litter) were evaluated for visceral changes (microdissection). These were decapitated and the heads placed in Bouin's for evaluation. After internal examination, the fetuses were eviscerated, placed in cassettes and stored in 70% ethanol.

The only external findings during an examination of all fetuses from the four groups were the following:

10 mg/kg: One fetus had an umbilical hernia. A second fetus had edema of the cervical and thoracic regions, absence of ear folds, small eye bulges, micromelia with absence of digits (fore- and hindlimbs), cleft in abdominal musculature and absence of anal opening as well as genital tubercle. These findings are not considered to be treatment related.

All other external, visceral or head findings were similar in all groups, were of a relatively minor nature or were in such few specimens that they did not appear to be the result of test article administration.

2. Skeletal

The remaining fetuses from each litter were sacrificed by ether, eviscerated and processed for skeletal examination using Alizarin Red S. They were examined under a dissecting microscope and then stored in glycerin.

Skeletal examination of fetuses did not reveal any indication that the administration of the test article had any effects.

The Reviewer has no comments regarding the methods and materials of this Report.

Historical control data were included in the Report (Report pages 437-445).

Detailed statistical analysis procedures were described in the report.

A Good Laboratory Practice Compliance Statement, a Quality Assurance Statement and a list of Quality Assurance inspections were included in the report.

The Registrant stated that the criteria of 40 CFR 158.34 for flagging studies for potential adverse effects were applied to the results of this study and that the study neither meets nor exceeds any of the applicable criteria. This Reviewer agrees.

II. DISCUSSION

Body weight gain was reduced during dosing at 500 mg/kg. There was also the possibility of a lower weight gain at the 100 mg/kg dose during this same period (days 6-16 of gestation). Food consumption was reduced at 100 and 500 mg/kg during dosing, essentially paralleling the decreases in body weight gain.

At 500 mg/kg, there was staining of the skin/fur in the anogenital area and/or an increase in the incidence of soft stools.

There appeared to be a decrease in group mean fetal body weights at the high dose of 500 mg/kg.

None of the treated groups showed any external, visceral or skeletal changes which were considered to be related to test article administration.

III. CONCLUSION

Methanearsonic acid was administered by gavage to pregnant rats at doses of 0, 10, 100 and 500 mg/kg on gestation days 6 through 15. The results were as follows:

10 mg/kg - maternal = none
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100 mg/kg - maternal = slight decrease in body weight gain and food consumption during the dosing period
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This study satisfies the Guideline Requirements (§83-3A) for a developmental toxicity study in rats.