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

JUL 1 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

CERTIFIED MAIL

E. M. Bellet, Ph.D.
Chemical Consultants International, Inc.
7270 West 98th Terrace, Suite 100
Overland Park, Kansas 66212

SUBJECT: Review of acute data for monosodium methanearsonate (MSMA) and disodium methanearsonate (DSMA).

Dear Dr. Bellet:

The acute studies for the reregistration of monosodium methanearsonate (MSMA) and disodium methanearsonate (DSMA) which you submitted on April 30 and May 22 1991, have been reviewed and the Agency's conclusions are as follows:

81-1 acute oral toxicity - rat (MRID 41892004)

This study satisfies the guideline requirements for an acute oral LD_{50} study in rats. An oral (gavage) LD_{50} study was conducted in male and female rats with disodium methanearsonate (DSMA) 81 P (technical) at doses of 1,000, 1,600 and 2,500 mg/kg. During the 14-day observation period, survivors of the 1,000 mg/kg dose were 5 out of 5 males and 5 out of 5 females; for the 1,600 mg/kg dose survivors were 4 out of 5 males and 3 out of 5 females, for the 2,500 mg/kg dose survivors were 1 out of 5 males and 1 out of 5 females. Some or all of the following clinical signs were reported for all doses: decreased activity, diarrhea, chromodacyorrhea, piloerection, abnormal gait, abnormal stance, decreased muscle tone and dyspnea.

The LD_{50} with 95% confidence limits was 2005.4 mg/kg (1605.7 - 2504.6) for males, 1841.3 mg/kg (1383.1 - 2451.2) for females and 1934.8 (1630.9 - 2295.2) for the combined males and females.

81-2 acute dermal toxicity - rabbit (MRID 41892005)

This study satisfies the guideline requirements for an acute dermal toxicity in rabbits. DSMA 81 P (technical) at a reported 81% administered to the skin of 5 male and 5 female rabbits for 24 hours (with a 14-day observation period) at 2,000 mg/kg (Limit

Dose), did not cause any deaths. The one female which died on day 13 was diagnosed as having "moderate coccidia infection". The only clinical sign reported was "Very slight to severe erythema at the application site was also observed throughout the study."

The LD_{50} was greater than 2,000 mg/kg (Limit Dose). The Toxicity Category is III.

81-2 acute dermal toxicity - rabbit (MRID 41890001)

This study satisfies the guideline requirements for an acute dermal toxicity in rabbits. Monosodium methanearsonate 51% administered to the skin of 5 male and 5 female rabbits for 24 hours (with a 14-day observation period) at 2,000 mg/kg (Limit Dose), did not cause any deaths. The primary clinical observation was decreased muscle tone in 4 to 6 of the 10 rabbits on observation days 5 through 9. There was skin necrosis at the application sites. Six of the 10 animals lost weight at the day-7 interval, but by day 14, all weighed more than initially.

The LD_{50} was greater than 2,000 mg/kg (Limit Dose). The Toxicity Category is III.

81-3 acute inhalation toxicity - rats (MRID 41892006)

This study satisfies the guideline requirements for an acute inhalation toxicity in rats study. DSMA administered by whole body inhalation for 4 hours (14-day observation period) to male and female rats at 6.0 mg/l, caused no deaths, clinical signs of respiratory and secretory irritation, body weight loss the first day post-exposure and lung discoloration in 4 of the 10 rats at necropsy.

81-4 primary eye irritation - rabbit (MRID 41892007)

This study satisfies the guideline requirements for primary eye irritation in rabbits. DSMA 81 P (technical) at a volume of 0.1 ml, was placed in the conjunctival sac of the right eye of 3 male and 3 female rabbits. Cornea, iris and conjunctival observations were recorded for 7 days. The primary effect of the test article was the appearance of redness and chemosis of the conjunctivae. These findings reverted to "normal" on observation day 7. The test article was considered to be an eye irritant.

81-5 primary dermal irritation - rabbit (MRID 41892008)

This study does not satisfy the guideline requirements for primary dermal irritation in rabbits. DSMA 81 P (technical) at an amount of 500 mg, was kept in contact with the skin (fur clipped) of 6 male rabbits for 4 hours. A 72-hour observation period followed. No erythema or edema was reported. The acute dermal toxicity study in rabbits (MRID 41892005) reported, "Very slight to severe erythema at the appliction site was also

observed throughout the study." This primary dermal irritation study in rabbits (MRID 41892008) did not report any erythema or edema. You must respond to what appears to be a difference in observations between the two studies. If the Agency accepts your explanation, the study will be upgraded to an acceptable study. This data must be submitted within 90 days of your receipt of this letter or if the study cannot be upgraded you must conduct a new study which is due June 30, 1993. If you do not submit the data within the specified time frame, I will have to consider appropriate regulatory action to ensure compliance with our statutory goals.

81-6 delayed contact hypersensitivity - guinea pig (MRID 41890002)

This study satisfies the guideline requirement for a delayed contact hypersensitivity in the guinea pig. MSMA 51% was administered to guinea pigs at 3 induction times (one week apart). This was followed by a challenge 2 weeks later. The positive control was DNCB and negative controls were 80% ethanol (induction) and 100% acetone (challenge). All DNCB animals showed positive responses at the second and third inductions as well as at challenge. One MSMA 51%/acetone guinea pig showed a grade of 1 at challenge. No hypersensitivity was reported.

81-6 delayed contact hypersensitivity - guinea pig (MRID 41892009)

This study satisfies the guideline requirement for a delayed contact hypersensitivity in the guinea pig. DSMA 81 P was administered to guinea pigs at 3 induction times (one week apart). This was followed by a challenge 2 weeks later. The positive control was DNCB and negative controls were 80% ethanol (induction) and 100% acetone (challenge). In the DSMA 81 P (technical) group, one male was sacrificed because of a prolapsed rectum and one male was found dead. Neither of these was considered treatment related. All DNCB animals showed positive responses at the second and third inductions (two of the five animals showed "+" at the first induction) as well as at challenge. No hypersensitivity was reported.

82-2 21-day dermal toxicity study - rabbits (MRID 41872701)

This study does not satisfy the guideline requirements for a 21-day dermal toxicity study in rabbits. The following report pages were illegible and must be replaced: clinical chemistry, pages 329-360; hematology, pages 402-433; and urine chemistry, pages 475-482. Analytical data regarding test article purity and stability must be provided in order to upgrade this into an acceptable study. This data must be submitted within 90 days of your receipt of this letter.

Although there were slight differences between treated and control groups regarding some hematologic and blood chemistry parameters, no definitive findings were considered related to treatment. Urinalysis findings were similar for all groups.

Gross pathology, organ weights (absolute, relative to body weights or relative to brain weights) and microscopic pathology did not appear to be affected by dermal administration of methanearsonic acid.

Methanearsonic acid was placed on the intact skin of the back (hair clipped) of rabbits at doses of 0 (deionized water control), 100, 300 and 1,000 mg/kg for 6 hours (occlusive dressing) 5 days/week for 3 weeks. All rabbits survived the 21-day study. There were no clinical signs nor apparent effects of test article administration.

The Systemic Toxicity No Observed Effect Level (NOEL) was 1,000 mg/kg (Limit Dose). A Systemic Toxicity Lowest Observed Effect Level (LOEL) of greater than 1000 mg/kg, HDT, was not attained. The Dermal Toxicity No Observed Effect Level (NOEL) was 1,000 mg/kg (Limit Dose). A Dermal Toxicity Lowest Observed Effect Level (LOEL) of greater than 1000 mg/kg, HDT, was not attained.

Copies of the DER's are attached. If you have any questions regarding this letter, please call Betty Crompton in the Accelerated Reregistration Branch at (703) 308-8067.

Sincerely,

Barbara L. Briscoe, Section Chief
Accelerated Reregistration Branch
Special Review and
Reregistration Division

cc: Alan C. Levy HED
Cynthia Giles RD PM

Reviewed By: Alan C. Levy, Ph.D. Alan C. Levy 5-18-92 005025
Section IV, Tox. Branch II (H7509C)

Secondary Reviewer: Elizabeth A. Doyle, Ph.D. E A. Doyle 5/15/92
Section IV, Tox. Branch II (H7509C)

DATA EVALUATION REPORT

Study Type: 21-Day Dermal Toxicity Study - Rabbits (§82-2)

Test Material: Methanearsonic Acid

Synonyms: monosodium acid methanearsonate

Tox. Chemical No.: 582 **MRID No.:** 418727-01
Identification No.: 013803-042519 **HED Project No.:** 1-1901

Sponsor: MAA (MSMA/DSMA) Research Task Force Three
Luxembourg Industries (Pamol), Ltd.
Tel Aviv, Israel

Testing Facility: Pharmakon Research International, Inc.
Waverly, PA

Title of Report: Methanearsonic Acid - 21-Day Dermal Toxicity Study in Rabbits

Study Number: PH 430-LI-001-90

Authors: Dennis J. Margitich and Larry J. Ackerman

Report Issued: March 13, 1991

Conclusions:

Methanearsonic acid was placed on the intact skin of the back (hair clipped) of rabbits at doses of 0 (deionized water control), 100, 300 and 1,000 mg/kg for 6 hours (occlusive dressing) 5 days/week for 3 weeks. There did not appear to be any skin changes or other definitive effects caused by test article administration.

Systemic Toxicity No Observed Effect Level (NOEL) = 1,000 mg/kg (Limit Dose)
Systemic Toxicity Lowest Observed Effect Level (LOEL) = not attained (>1,000 mg/kg, HDT)

Dermal Toxicity No Observed Effect Level (NOEL) = 1,000 mg/kg
Dermal Toxicity Lowest Observed Effect Level (LOEL) = not attained (>1,000 mg/kg, HDT)

Classification: Core Supplementary - The Registrant needs to provide replacement pages and analytical data acceptable to the Agency in order to upgrade this Report to Core Minimum.

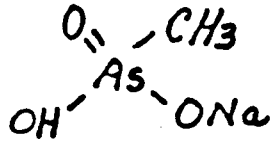
This study does not satisfy the Guideline Requirements (§82-2) for a 21-day dermal toxicity study in rabbits.

I. MATERIALS AND METHODS

A. Test Article

Name: Methanearsonic acid, monosodium acid methanearsonate

Formula:



Lot Number: 0030401 (Batch Number)
Purity: 99.44%
Appearance: white crystalline flake

Vehicle: deionized water (control group only - 1 ml)

B. Animals

Albino New Zealand White Rabbits from Hare-Marland, Hewitt, NJ were used in this study. There was a 10 day period of acclimation. The animals weighed 2.05-2.56 kg at study initiation and were assigned to treatment groups according to body weights by a table of random numbers. Rabbits were individually housed. "Every attempt was made to maintain a temperature of 20°C ± 3°C (63°F to 74°F) and a humidity of 30 to 70%." "Temperature and humidity readings were within range throughout the study." There was a 12 hour light/dark cycle. Food and water were available ad libitum.

C. Dosing

Four groups of animals (5/sex/group) received 0 (vehicle control, deionized water), 100, 300 and 1,000 (Limit dose) mg/kg of the test article. Dosing was 5 days/week for 3 weeks.

At least 10% of the dorsal surface of collared rabbits had hair removed by clipping (repeated as necessary). The test article was applied to the intact skin as received from the Sponsor (white crystalline flake). Gauze patches, moistened with 1 ml of deionized water were then applied to the site. A rubber dam was placed over the patches and the animal was wrapped with an elastic bandage held in place with tape. After 6 hours of exposure, the wrappings, dam and gauze were removed and the test site wiped to remove test article.

D. Observations

1. Skin - Sites were observed daily prior to dosing as as well as at terminal sacrifice for signs of erythema and edema (scored by the Draize Method - page 90 of the Report).

2. Clinical Signs - Observations were made at least once daily for toxicologic/pharmacologic signs. Mortality checks were made twice daily.

3. Body Weights - These were recorded initially, weekly and at terminal necropsy. Dosing (mg/kg) was based on the most recent body weight.

4. Food Consumption - This was measured on days 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20.

5. Clinical Laboratory - Blood samples for hematology and chemistry were obtained from the central ear artery (pretest) or from cardiac puncture (at sacrifice) after an overnight fast. Urine was collected prior to study initiation and at termination. [NOTE: No collection details were provided in the report.]

   a. Hematology - The following parameters were examined:

Hemoglobin	Platelet Count
Hematocrit	Mean Corpuscular Volume
Erythrocyte Count	Mean Corpuscular Hemoglobin
Total Leucocyte Count	Mean Corpuscular Hemoglobin
Differential Leucocyte count	Concentration

   b. Chemistry - The following parameters were examined:

A/G Ratio	Serum Aspartate Aminotransferase
Calcium	Urea Nitrogen
Phosphorus	Albumin
Chloride	Blood Creatinine
Sodium	Total Bilirubin
Potassium	Total Serum Protein
Fasting Glucose	Total Cholesterol
Serum Alanine Aminotransferase	

c. Urine - The following parameters were examined:

Occult Blood	Total Bilirubin
Protein	Urobilirubin
Ketone Bodies	Sediment
Appearance	Specific Gravity
Glucose	pH

6. Gross Pathology - All surviving animals were euthanitized by intravenous sodium pentobarbital. A necropsy was performed on all rabbits. The following organs were weighed (weights expressed as absolute, relative to body weight and relative to brain weight): gonads, adrenals, brain, kidneys and liver.

7. Microscopic Pathology - Organs/tissues from the terminal sacrifice were preserved in 10% neutral buffered formalin for "possible future histopathological examination." Evaluation was performed on treated and untreated skin as well as on organs/tissues from all control and high-dose terminally sacrificed animals. The following tissues were preserved:

Gross Lesions	Pancreas	Ileum
Brain (medulla/pons) cerebellar & cerebral cortex	Testes	Cecum
	Ovaries	Colon
	Uterus	Rectum
Pituitary	Epididymides	Gallbladder
Thyroid/parathyroid	Prostate	Urinary Bladder
Thymus	Seminal Vesicles	Cervical Lymph Node
Lungs	Aorta	Mammary Gland
Trachea	Skin (treated & untreated)	Thigh Muscle
Heart		Peripheral Nerve
Sternum (marrow)	Tongue	Eyes
Salivary Glands	Esophagus	Femur
Liver	Nasal Turbinates	Spinal Cord (3 levels)
Spleen	Stomach	Lachrymal Glands
Kidneys	Duodenum	
Adrenals	Jejunum	

II. RESULTS

A. Test Article Purity and Stability

N O T E: Page 13 of the Report states: "The purity, identity, strength and stability of the test article were the responsibility of the Sponsor. Samples of the test article were not required to be submitted to the sponsor for stability analysis, as analysis was previously performed."

Page 547 of the Report is a "Certificate of Analysis" from Luxembourg Industries (PAMOL) Ltd. This certifies that Methanearsonic Acid - Tech (MAA), Batch 0030401 sent to Pharmakon Research International, Inc., "... has gone through quality control procedures, and was found to meet all specifications." The assay % w/w stated to be "99.44%".

R E V I E W E R' S C O M M E N T: No analytical data regarding purity or stability were presented in this report. Therefore, the study is considered to be Core Supplementary. If the Registrant provides these analytical data and they are acceptable to the Agency, the Study will be upgraded to Core Minimum.

B. Mortality and Clinical Observations

1. Mortality - All rabbits survived until terminal sacrifice after 21 days.

2. Toxicologic/Pharmacologic Signs - There were none which were attributed to test article administration.

3. Skin - No erythema or edema was reported for any animal at any observation time.

C. Body Weights

Body weight and weight gain data are summarized in Table 1.

There were no statistically significant ($p<0.05$ or $p<0.01$) differences in body weights or weight gains between any treated group and the respective control for males or females at any interval. The variations in weight gains and the standard deviation ranges shown in Table 1 indicate the amount of variation of these values within a group as well as from group-to-group. It is not considered that there was any biological difference in body weights or weight gains that were caused by test article administration.

Table 1

A SUMMARY OF GROUP MEAN BODY WEIGHTS AND WEIGHT GAINS IN A 21-DAY DERMAL RABBIT STUDY WITH METHANEARSONIC ACID

Day	Males mg/kg = 0	100	300	1000	Females 0	100	300	1000
BODY WEIGHTS (kg)								
0	2.4	2.4	2.4	2.3	2.2	2.2	2.2	2.2
7	2.6	2.5	2.5	2.4	2.4	2.3	2.4	2.3
14	2.7	2.7	2.6	2.6	2.6	2.5	2.6	2.4
20	2.7	2.7	2.8	2.7	2.7	2.6	2.7	2.5
BODY WEIGHT GAIN (g)								
0-7	142	102	103	133	165	13	113	101
7-14	100	105	164	144	221	198	203	100
14-20	54	64	122	81	62	129	119	128
0-20	296	271	389	358	448	340	435	329

NOTE: Standard Deviation ranges (g) for body weights - males = 80-253; females = 93-289

Data extracted or calculated from Report Tables 1 and 2, pages 24-27.

D. Food Consumption

In males, all group mean values at all intervals were similar.

For females, one interval at 100 mg/kg and two intervals at 1,000 mg/kg were statistically ($p<0.05$ or $p<0.01$) lower than the control value. The data were presented as daily mean food consumption, and in almost all instances, the number of g of food consumed for the 3 dosed groups was numerically below the control figures. The test article appeared to have little or no effect on food consumption.

E. Hematology

The only statistically significant differences were in males and were reported to be as follows: mean corpuscular hemoglobin concentration lower at 300 mg/kg, monocytes lower at 300 and 1,000 mg/kg. None of these were considered to be test article related or of biological significance.

There were no differences noted in any other parameters in males.

Group mean hemoglobin and hematocrit values suggested slight anemia in females at 1,000 mg/kg (See Table 2). However, a review of individual animal data indicated that this observation was primarily due to one rabbit, No. 5036 (Table 3).

Table 2

SELECTED HEMATOLOGIC PARAMETERS IN FEMALE RABBITS ADMINISTERED METHANEARSONIC ACID DERMALLY FOR 21-DAYS

Dose mg/kg	Baseline			Terminal		
	Erythroc	Hematocr	Hemoglob	Erythroc	Hematocr	Hemoglob
0	6.5±0.4	43±2.4	13.9±0.6	5.8±0.6	39±2.9	12.4±1.0
100	5.6±0.6	38±3.9	12.5±1.0	5.2±0.5	35±2.5	11.2±0.6
300	5.9±0.3	39±1.1	12.8±0.3	5.4±0.7	37±3.8	11.6±1.3
1,000	6.3±0.5	41±3.5	13.1±1.0	5.1±0.8	33±4.3	10.7±1.1

Erythroc = Erythrocytes ($10^6/mm^3$)
Hematocr = Hematocrit (%)
Hemoglob = Hemoglobin (g/dl)
NOTE: Values are group means ± standard deviations for 5 females
Data extracted from Report Table 10, pages 72 and 73.

Table 3

INDIVIDUAL ANIMAL VALUES FOR ERYTHROCYTES, HEMATOCRIT AND HEMOGLOBIN PARAMETERS IN RABBITS ADMINISTERED METHANEARSONIC ACID AT 1,000 MG/KG FOR 21 DAYS

Parameter	No. =	Baseline					Terminal				
		5036	5037	5038	5039	5040	5036	5037	5038	5039	5040
Eryth ($10^6/mm^3$)		5.9	QNS	6.3	6.0	7.0	3.8	5.8	5.6	5.5	4.9
Hematocrit (%)		40	QNS	41	38	46	27	37	37	34	31
Hemogl (g/dl)		12.8	QNS	13.3	12.0	14.3	9.1	12.0	11.4	10.9	10.2

Eryth = Erythrocyte Hemogl = Hemoglobin
QNS = Quantity Not Sufficient
Data extracted from Report pages 397-401.

F. Blood Chemistry

In spite of several instances of statistically significant differences between treated and control group mean values for several parameters, the only data which are considered suggestive of a test article effect were a decrease in group mean cholesterol levels. (See Table 4)

Table 4

INDIVIDUAL ANIMAL VALUES FOR CHOLESTEROL IN RABBITS ADMINISTERED METHANEARSONIC ACID FOR 21 DAYS

Dose	Baseline					Group	Terminal					Group
mg/kg	#1	#2	#3	#4	#5	Mean	#1	#2	#3	#4	#5	Mean
MALES												
0	52	46	55	69	71	59	36	46	72	35	37	45
100	26	44	68	69	37	49	22	36	33	41	27	32
300	59	48	64	136	70	75	35	28	13	22	36	27*
1,000	177	75	84	50	72	92	23	24	35	12	15	21**
FEMALES												
0	38	88	163	46	52	77	26	36	22	33	36	31
100	84	57	71	39	80	66	33	32	24	10	19	24
300	70	72	75	61	57	67	26	27	26	9	12	20
1,000	49	76	38	62	85	62	29	55	22	46	37	38

NOTE: Cholesterol values = mg/dl
= rabbit numbers 1, 2, 3, 4 and 5
Historical Control Range = 53-117 (Report page 287)
Data extracted from Report pages 289-328.

Because of the individual values presented in Table 4, it is felt that a definitive test article effect cannot be made.

G. Urinalysis

There were no parameters which were considered to be affected by the administration of Methanearsonic acid.

H. Pathology

1. GROSS - There were no gross pathology findings at necropsy which appeared to be test article related.

2. ORGAN WEIGHTS - A statistically significant ($p<0.05$ or 0.01) increase in female kidney to body weight ratio at 100 mg/kg and for female liver to body weight ratios at 100 and 1,000 mg/kg was observed. These data are not considered to be definitive regarding a test article effect.

3. MICROSCOPIC - The pathology report stated, "When compared to the control rabbits, the administration of 1,000 mg/kg of Methanearsonic acid, as used in this study, did not cause any dermal irritation at the treatment

site nor any systemic toxicity in the full screen of tissues evaluated."

- -

REVIEWER'S COMMENTS

1. The following report pages were illegible and must be replaced: clinical chemistry, pages 329-360; hematology, pages 402-433; and urine chemistry, pages 475-482.

2. Analytical data regarding test article purity and stability need to be provided by the Registrant.

Classification of this Report: This Report is considered to be Core Supplementary. Submission of the replacement pages and analytical data would allow this Report to be upgraded to Core Minimum, provided they are acceptable to the Agency.

The Reviewer has no other comments regarding the Methods and Materials section of the Report.

Brief statements regarding statistical methodology were included in the Report.

A Good Laboratory Practice Compliance statement, A Quality Assurance statement and the Quality Assurance inspection dates were included.

III. DISCUSSION

Analytical data regarding test article purity and stability need to be provided by the Sponsor.

All rabbits survived the 21-day study. There were no clinical signs nor apparent effects of test article administration on treated skin (no erythema or edema).

Although there were slight differences between treated and control groups regarding some hematologic and blood chemistry parameters, no definitive findings were considered related to treatment. Urinalysis findings were similar for all groups.

Gross pathology, organ weights (absolute, relative to body weights or relative to brain weights) and microscopic pathology did not appear to be affected by dermal administration of methanearsonic acid.

IV. CONCLUSION

Methanearsonic acid was placed on the intact skin of the back (hair clipped) of rabbits at doses of 0 (deionized water control), 100, 300 and 1,000 mg/kg for 6 hours (occlusive dressing) 5 days/week for 3 weeks. There did not appear to be any skin changes or other definitive effects caused by test article administration.

Systemic Toxicity No Observed Effect Level (NOEL) = 1,000 mg/kg (Limit Dose)

Systemic Toxicity Lowest Observed Effect Level (LOEL) = not attained (>1,000 mg/kg, HDT)

Dermal Toxicity No Observed Effect Level (NOEL) = 1,000 mg/kg (Limit Dose)

Dermal Toxicity Lowest Observed Effect Level (LOEL) = not attained (>1,000 mg/kg, HDT)

Classification: Core Supplementary (Registrant needs to provide replacement pages and analytical data acceptable to the Agency in order to upgrade this Report to Core Minimum).

This study does not satisfy the Guideline requirements (§82-2) for a 21-day dermal toxicity study in rabbits.