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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM:

Subject: Review of Toxicology Studies with Methanearsonic Acid/Methanearsonic acid, monosodium salt to support reregistration of the test substance. (Toxchem Number 582, HED Project No. 2-0879; Barcode number: D172561)

FROM: Steven L. Malish, Ph.D., Toxicologist S.L. Malish 3/15/92
Tox. Branch II, Review Section IV
HED (H7509C)

TO: Barbara Briscoe PM (51)/Betty Crompton PM Team Reviewer
Special Review and Reregistration Division
HED (H7508W)

THRU: Elizabeth Doyle, Ph.D., Section Head E.A. Doyle 3/17/92
Tox. Section II, Review Section IV
HED (H7509C)

and

Marcia van Gemert, Ph.D., Branch Chief
Tox. Branch II
HED (H7509C) M. van Gemert 3/18/92

ACTION REQUESTED: Review of toxicology study for reregistration requirements for MRID 420105-01, Guideline 85-1.

Study Summarized

MRID 420105-01, Metabolism Study (85-1); Core - guideline

Sprague-Dawley CD rats were treated by oral gavage with a single dose of [^{14}C-methyl]MSMA at doses of 0 (control), 5 or 200 mg/kg, 5 mg/kg MSMA orally for 14 consecutive days followed by a single oral dose of 5 mg/kg of [^{14}C-methyl]MSMA or a single i.v. injection of 5 mg/kg of [^{14}C-methyl]MSMA.

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[^{14}C-methyl]MSMA was excreted in the urine and feces 24-48 hours after treatment, primarily as unchanged parent. The mean total radiocarbon recovered as $^{14}CO_2$ accounted for $\leq$0.5% of the administered dose in all treated groups.

During the 7 days following dosing, the mean total recovery of radiocarbon in urine and feces was 91.3% for males and 88.8% for females. Specifically, the oral dose group (both sexes) excreted a mean of 41% of the administered dose in the urine and 48% in the feces; the i.v. group excreted 91% of the radiocarbon in the urine. Comparison of the radiocarbon excreted in the urine by the i.v. dosed rats with that excreted by the orally dosed rats indicated that approximately half of the oral dose was absorbed by the low and consecutive dose groups and somewhat less by the high dose group.

A mean of 10, 6, 13 and 3% of the administered dose remained, respectively, in the tissues and carcass at the 5 mg/kg, 200 mg/kg, consecutive and i.v infusion dose groups. In all groups, the largest fraction of the bound radiocarbon was accounted for in the blood; other organs contained lesser amounts.

Total mean recovery of radiocarbon in all treated groups was 98.2% of the administered dose.

Reviewed by Steven L. Malish, Ph.D. S.L. Malish 3/16/92
Tox Branch II, Section IV (7509C)
Secondary Reviewer: Elizabeth Doyle, Ph.D. E.A. Doyle 3/17/92
Tox. Branch II, Section IV (H7509C)

DATA EVALUATION REPORT

STUDY TITLE: Metabolism Study (85-1)

MRID NO.: 420105-01

TEST MATERIAL: [^{14}C-methyl]monosodium methanearsonate; monosodium methanearsonate

SYNONYM: [^{14}C-methyl]MSMA; MSMA

SPONSOR: MAA(MSMA/DSMA)Research Task Force 3
Luxembourg Industries (PAMOL), Ltd.
27 Hamered Street
P.O. Box 13
Tel Aviv 61000, Israel

LABORATORY: PTRL East, Inc.
3945 Simpson Lane
Richmond, Kentucky 40475

REPORT NO.: PTRL Report No. 1344

REPORT TITLE: Absorption, Distribution and Elimination of [^{14}C-methyl]MSMA in the Rat

AUTHORS: N. Wells-Gibson, B.S., J. D. Marsh, M.S., G. R. Krautter, M.S.

REPORT ISSUED: August 30, 1991

CONCLUSIONS:

Sprague-Dawley CD rats were treated by oral gavage with a single dose of [^{14}C-methyl]MSMA at doses of 0 (control), 5 or 200 mg/kg, 5 mg/kg MSMA orally for 14 consecutive days followed by a single oral dose of 5 mg/kg of [^{14}C-methyl]MSMA or a single i.v. injection of 5 mg/kg of [^{14}C-methyl]MSMA.

[^{14}C-methyl]MSMA was excreted in the urine and feces 24-48 hours after treatment, primarily as unchanged parent. The mean total radiocarbon recovered as $^{14}CO_2$ accounted for $\leq$ 0.5% of the administered dose in all treated groups.

During the 7 days following dosing, the mean total recovery of radiocarbon in urine and feces was 91.3% for males and 88.8% for females. Specifically, the oral dose group (both sexes) excreted a

mean of 41% of the administered dose in the urine and 48% in the feces; the i.v. group excreted 91% of the radiocarbon in the urine. Comparison of the radiocarbon excreted in the urine by the i.v. dosed rats with that excreted by the orally dosed rats indicated that approximately half of the oral dose was absorbed by the low and consecutive dosed animals and somewhat less by the high dosed animals.

A mean of 10, 6, 13 and 3% of the administered dose remained, respectively, in the tissues and carcass at the 5 mg/kg, 200 mg/kg, consecutive and i.v infusion dose groups. In all groups, the largest fraction of the bound radiocarbon was accounted for in the blood; other organs contained lesser amounts.

Total mean recovery of radiocarbon in all treated groups was 98.2% of the administered dose.

CLASSIFICATION: Core: guideline

This study satisfies the guideline requirements (85-1) for a metabolism study.

TEST MATERIAL:	Chemical:	[^{14}C-methyl]monosodium methanearsonate (labeled); monosodium methanearsonate (unlabeled)
	Lot:	labeled: ICN CFO 2289, GPS/2/79/1, PTRL No. 457-3 (≥99.4% purity); unlabeled: ASC 66878-0101, PTRL No. 468-9 (100.9% purity); ASC 66878-0102; PTRL No.481-35 (100.2% purity).
	Spec. Act:	2.4 mCi/mM
	Stability:	stable
	Storage:	-20°C.
TEST ANIMALS:	Species:	rat
	Strain:	Sprague-Dawley CD^{R}(Crl:CDBR)
	Sex:	male/female
	Groups:	4 treated groups of 5 animals/sex, 1 control group of 3 animals/sex
	Age:	6 - 10 weeks at initiation
	Weight:	200 - 250 gms at initiation
	Source:	Portage MI facility of Charles River Labs, Inc. Wilmington, MA.

Quality Assurance - A quality assurance statement was issued.

MATERIALS AND METHODS:

Animals were acclimated for at least 7 days before being placed on

test. Certified Rodent Chow #5002 (Purina Mills, Inc.) and water was provided ad libitum. Animals in each dose group were assigned by random numbers in ascending order.

Study Design

Rats were treated by oral gavage with a single dose of [^{14}C-methyl]MSMA at 0 (control), 5 or 200 mg/kg, 5 mg/kg MSMA orally for 14 consecutive days followed by a single oral dose of 5 mg/kg of [^{14}C-methyl]MSMA or a single dose of 5 mg/kg of [^{14}C-methyl]MSMA by i.v. injection.

Four (4) treated groups consisted of 5 animals/sex. The vehicle control group consisted of 3 animals/sex. Treatment groups were placed on test one group at a time and were dosed by oral intubation (feeding needle) or by i.v. injection of the test substance into the femoral vein (Table 1).

Immediately following the dose of the radiolabeled test substance or control vehicle, the animals were transferred to individual glass metabolism cages designed to separate and collect urine, feces and expired air (for $^{14}CO_2$) and to quantify feed and water consumption.

Table 1

Dose Group Treatments[1]

	Group	Dose[2] (mg/kg)	No. of Rats/Sex	Route
1.	Control	Vehicle	3 M/F	oral intubation
2.	Single Oral	5.0	5 "	oral intubation
3.	Single Oral	200.0	5 "	oral intubation
4.	Consecutive[3]	5.0	5 "	oral intubation
5.	Single i.v.	5.0	5 "	i.v.

[1]Adapted from original report p. 16.
[2]The amount of vehicle (water) received by each rat was approximately 2.5 - 4.5 ml/kg.
[3]Rats received a single 5.0 mg/kg oral dose of [^{14}C-methyl]MSMA within 24 hours after pre-treatment with 14 consecutive oral doses of unlabeled MSMA given at 5.0 mg/kg/day.

In all treated groups, the excretion of radiocarbon in feces and urine was sampled at 0.5 and 1 thru 7 days postdose. Carbon dioxide was sampled at 0.5 and 1 day postdose.

At the time of sacrifice, 7 days after treatment with [^{14}C-methyl]MSMA or vehicle control, animals were anesthetized and exsanguinated by aortic puncture. Residual radiocarbon levels were

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quantified by radioassay in the blood, bone, brain, fat (visceral), heart, kidney, liver, lungs, muscle (thigh), ovary, skin (clipped), spleen, testis, uterus and the residual carcass.

Combustion Analysis and Radioassay:

Urine, feces, blood and tissue samples were combusted to carbon dioxide, water and inorganic ash using a sample oxidizer. The radiocarbon from the combustion products were quantitated by liquid scintillation spectrometry. The expired air $^{14}CO_2$ was similarly assayed.

Statistical Analysis:

Mean and standard deviations were calculated.

Urine and Feces Sample Compositing for Metabolite Characterization

After the material balance from each definitive dose group was established, the urine and feces from each sex of each group was composited for metabolite characterization.

Extraction of Feces and Blood

Composited feces samples from each dose group/sex were extracted in phosphate buffer followed by extraction in n-hexane. The small amount of unextracted solids were then hydrolyzed by refluxing with hydrochloric acid. Extracts were quantitated by direct radioassay and analyzed for metabolites by HPLC.

Composited whole blood samples from the 200 mg/kg dose males and females were extracted with acetonitrile followed by water extraction, quantitated by direct radioassay and analyzed for metabolites by HPLC.

High Performance Liquid Chromatography (HPLC)
Whole rat urine, feces and blood extracts were analyzed for metabolites by HPLC.

Thin Layer Chromatography (TLC)

Metabolite identification in the whole urine and feces extracts were confirmed by thin layer chromatography.

RESULTS AND DISCUSSIONS:

Animal Observations

There were no signs of toxicity observed in any of the treated groups during the in vivo portion of the study.

Material Balance Studies

[^{14}C-methyl]MSMA was readily excreted in the urine and feces of all dose groups within 24-48 hours after treatment (Tables 2 thru 5). The mean total radiocarbon recovered as $^{14}CO_2$ accounted for $\leq$ 0.5% of the administered dose (Tables 2 thru 5).

For most of the oral dose groups (5 and 200 mg/kg and consecutive dosed females) mean total radiocarbon excreted in the feces was slightly higher than that excreted in the urine. The consecutive dosed group males excreted slightly more radiocarbon in the urine. In contrast, the i.v. dosed group excreted the majority of the radiocarbon in the urine (Tables 2 thru 6).

When comparing the amounts of radiocarbon excreted in the urine versus the feces, excretion patterns were similar between the oral 5 mg/kg and consecutive dose groups. However, when comparing the excretion patterns of the 5 mg/kg dose to the 200 mg/kg dose, the 200 mg/kg animals excreted approximately 10% more of the administered dose in the feces. This probably reflects less complete absorption at 200 mg/kg than at 5 mg/kg. In contrast, virtually all of the injected radiocarbon was excreted in the urine (Table 2 thru 6)

The total recovery of radiocarbon in urine, feces, expired air and tissues for all treated groups was 98.2% of the administered dose. Specifically, mean total recovery for the 5 and 200 mg/kg, consecutive and i.v. dosed group was 96.5, 101.1, 97.5 and 97.8%, respectively (Tables 2 thru 5).

Table 2

Cumulative Material Balance Summary for Rats Receiving a 5.0 mg/kg Oral Dose of [^{14}C-methyl]MSMA[1,2]

Day	Urine M/F %	Feces M/F %	CO_2 M/F %	Tissue M/F %	Total M/F %
0.5	34.8/34.6	25.8/17.1	0.5/0.4	--	61.1/52.2
1	39.9/40.0	43.1/40.3	0.7/0.6	--	83.8/81.0
2	40.8/41.0	45.3/43.8	"	--	86.8/85.4
3	41.1/41.1	45.4/43.9	"	--	87.2/85.6
7	41.6/41.6	45.4/43.9	"	9.3/9.9	97.0/96.0

[1]Adapted from the original report, p. 55 thru 58.
[2]Mean values, statistical analyses not performed.

Table 3

Cumulative Material Balance Summary for Rats Receiving a Single 200 mg/kg Oral Dose of [^{14}C-methyl]MSMA[1,2]

Day	Urine M/F %	Feces M/F %	CO_2 M/F %	Tissue M/F %	Total M/F %
0.5	27.5/20.5	30.0/16.8	0.5/0.3	--	58.0/37.6
1	37.6/30.5	49.8/43.9	0.5/0.4	--	87.9/74.8
2	39.2/33.0	56.1/56.5	"	--	95.8/89.9
3	39.5/33.4	56.5/57.8	"	--	96.6/91.6
7	40.3/33.7	57.1/58.0	"	5.9/6.3	103.7/98.4

[1]Adapted from the original report, p. 59 thru 62.
[2]Mean values, statistical analyses not performed.

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Table 4

Cumulative Material Balance Summary for Rats Receiving 14 Consecutive Doses of 5.0 mg/kg MSMA Followed by a Single Oral Dose of 5.0 mg/kg [^{14}C-methyl]MSMA[1,2]

Day	Urine M/F %	Feces M/F %	CO_2 M/F %	Tissue M/F %	Total M/F %
0.5	40.5/30.4	25.7/12.1	0.4/0.4	--	66.6/42.9
1	45.4/35.4	35.0/33.5	0.4/0.4	--	80.8/69.3
2	46.3/37.2	38.1/44.8	"	--	84.8/82.4
3	45.6/37.7	38.2/44.8	"	--	85.2/82.9
7	47.4/38.3	38.3/44.8	"	11.9/13.6	97.9/97.1

[1]Adapted from the original report, p. 63 thru 66.
[2]Mean values, statistical analyses not performed.

Table 5

Cumulative Material Balance Summary for Rats Receiving a Single I.V. Infusion Dose of 5.0 mg/kg [^{14}C-methyl]MSMA[1,2,3]

Day	Urine M/F %	Feces M/F %	Tissue M/F %	Total M/F %
0.5	82.6/81.9	3.1/0.0	--	85.6/81.9
1	88.6/90.8	4.4/0.4	--	93.0/91.2
2	89.4/92.3	4.9/1.5	--	94.3/93.8
3	89.7/92.6	5.1/1.7	--	94.7/94.3
7	89.9/92.8	5.3/2.1	2.7/2.9	97.9/97.7

[1]Adapted from the original report, p. 67 thru 70.
[2]Mean values, statistical analyses not performed.
[3]No respiratory $^{14}CO_2$ recovered.

After 7 days post-treatment, the mean cumulative urinary excretion of administered radiocarbon for male and female animals at 5.0 mg/kg was 41.6%; at 200 mg/kg 40.3% and 33.7%; at the consecutive dose 47.4 and 38.3% and in the i.v. dose 89.9 and 92.8%, respectively. The mean total recovery of radiocarbon in urine and feces was 91.3% for males and 88.8% for females (Table 6).

Table 6

Urine and Feces Cumulative Excretion Pattern [^{14}C-methyl]MSMA 7 Days After Dosing[1,2]

Dose	Urine M/F %	Feces M/F %	Total M/F %
Single (5 mg/kg)	41.6/41.6	45.4/43.9	87.0/85.5
Single (200 mg/kg)	40.3/33.7	57.1/58.0	97.4/91.7
Consecutive[3]	47.4/38.3	38.3/44.8	85.7/83.1
Single i.v.	89.9/92.8	5.3/2.1	95.2/94.9

[1]Adapted from the original report. p. 58, 62, 66 and 70.
[2]Mean values, statistical analyses not performed.
[3]Rats received a single 5.0 mg/kg oral dose of [^{14}C-methyl]MSMA within 24 hours after pre-treatment with 14 consecutive oral doses of unlabeled MSMA given at 5.0 mg/kg/day.

Tissue levels

All animals were sacrificed 7 days after treatment with radiolabeled [^{14}C-methyl]MSMA or vehicle (control group) and tissue residues quantitated. The highest level of radioactivity were found in the blood. The blood contained (as a percentage in male/female) 3.2M/3.7F at 5 mg/kg; 2.3M/2.4F at 200 mg/kg; 3.7M/4.1F in the consecutive dose and 0.9% in both males and females in the i.v. infusion dose level. Lesser amounts were found in the tissues [e.g. up to 0.12% (liver), 0.24% (kidney) and 0.38% (spleen)].

Between 9.3M/9.9F; 5.9M/ 6.3F; 11.9M/13.6F and 2.7M/2.9F percent of the administered dose remained in tissues and the carcass of the 5.0 mg/kg, 200 mg/kg, consecutive and i.v. infusion groups, respectively (Tables 2 thru 5).

HPLC Metabolite Profiles of Rat Urine and Feces

A total of 3 metabolites were observed in the urine and/or feces samples. The major product excreted in both urine and feces was unchanged parent, accounting for 79.7 to 97.4% of the administered dose. A minor unknown metabolite product (unknown A was detected in the urine and feces of the low dose groups which accounted for 1.8 to 6.7% of the dose. This unknown metabolite was not excreted by the high dose group animals. A second unknown minor metabolite (unknown B) was detected in trace amounts (0.7%) in the urine of consecutively dosed animals (Table 7).

Table 7

Quantitation of Metabolites in Rats Dosed with [^{14}C-methyl]MSMA[1]

	Recovery as Percent of Dose							
	I.V. 5.0 mg/kg		Oral 5.0 mg/kg		Oral 200.0 mg/kg		Oral Consecutive plus 5.0 mg/kg[2]	
Metabolite	M	F	M	F	M	F	M	F
Unknown A	3.7	3.7	6.7	6.1	0.0	0.0	1.8	2.6
Unknown B	0.0	0.0	0.0	0.0	0.0	0.0	0.7	0.7
MSMA	92.8	91.5	80.3	79.7	97.4	91.7	83.2	79.7
Total	94.9	95.2	87.0	85.8	97.4	91.7	85.7	83.0

[1]Data from original report, p. 82.
[2]Rats received a single 5.0 mg/kg oral dose of [^{14}C-methyl]MSMA within 24 hours after pre-treatment with 14 consecutive oral doses of unlabeled MSMA given at 5.0 mg/kg/day.

Confirmatory TLC of Rat Urine and Feces Metabolites

All urine and fecal samples analyzed by HPLC were also analyzed by TLC. Quantitation of the sample spots that co-migrated with [^{14}C-methyl]MSMA as a percent of the administered dose, correlated closely with the values obtained from HPLC analysis. The results confirmed that the identity of the major metabolite in urine and feces was [^{14}C-methyl]MSMA.

Characterization of Blood Residues

Attempts were made to characterize the test material residues present in whole blood of the composited 200 mg/kg dose group. Extraction efficiencies for male and female blood samples were 55.5 and 23.6%, respectively.

The blood extract added to the HPLC column could not be eluted from the column. The nature of the bound residue remains unidentified.

CONCLUSIONS:

Sprague-Dawley CD rats were treated by oral gavage with a single dose of [^{14}C-methyl]MSMA at doses of 0 (control), 5 or 200 mg/kg, 5 mg/kg MSMA orally for 14 consecutive days followed by a single oral dose of 5 mg/kg of [^{14}C-methyl]MSMA or a single i.v. injection of 5 mg/kg of [^{14}C-methyl]MSMA.

[^{14}C-methyl]MSMA was excreted in the urine and feces 24-48 hours after treatment, primarily as unchanged parent. The mean total radiocarbon recovered as $^{14}CO_2$ accounted for ≤0.5% of the administered dose in all treated groups.

During the 7 days following dosing, the mean total recovery of radiocarbon in urine and feces was 91.3% for males and 88.8% for females. Specifically, the oral dose group (both sexes) excreted a mean of 41% of the administered dose in the urine and 48% in the feces; the i.v. group excreted 91% of the radiocarbon in the urine. Comparison of the radiocarbon excreted in the urine by the i.v. dosed rats with that excreted by the orally dosed rats indicated that approximately half of the oral dose was absorbed by the low and consecutive dosed animals and somewhat less by the high dosed animals.

A mean of 10, 6, 13 and 3% of the administered dose remained, respectively, in the tissues and carcass at the 5 mg/kg, 200 mg/kg, consecutive and i.v. infusion dose groups. In all groups, the largest fraction of the bound radiocarbon was accounted for in the blood. The other organs contained lesser amounts [e.g. up to 0.72% (liver), 0.24% (kidney) or 0.38% (spleen)].

Total mean recovery of radiocarbon in all treated groups was 98.2% of the administered dose. It is unclear, whether the residual bound radioactivity in tissues results from residual blood-bound radioactivity or from actual tissue-bound radioactivity.