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

009382

MAR 25 1992

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM:

Subject: Review of Toxicology Studies with Methanearsonic Acid to support reregistration of the test substance. (Toxchem Number 582, HED Project No. 2-1208; Barcode number: D173830)

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 Marcia van Gemert 3/18/92
Tox. Branch II
HED (H7509C)

ACTION REQUESTED: Review of toxicology studies for reregistration requirements.

Study Summarized

MRID 421732-01, Oncogenicity Study - mouse (83-2); Core - guideline.

Methanearsonic acid was incorporated into the diet of 5 groups of 52 mice/sex/group at concentrations of 0, 1.8, 9.3, 38 and 83 mg/kg/day (males) and 0, 2.2, 12, 46 and 104 mg/kg/day (females) for 104 weeks.

No evidence of carcinogenicity was seen.

Mortality was not affected by treatment. In the high and high intermediate dose animals of both sexes, signs of toxicity occurred after 10-12 weeks of treatment. Loose and mucoid feces were seen at the high dose. A decrease in the mean body weight gain and an increase water intake occurred in the high dose of both sexes and the high-intermediate dose females. Food consumption was increased in the high dose females.

The colon, cecum and rectum showed a slight degree of diffuse cuboidal and squamous metaplasia in both sexes at the high dose versus the control.

The MTD (Maximum Tolerated Dose) = 83 mg/kg/day (Highest Dose Tested) - males; 46 mg/kg/day - females.

NOEL (No observed effect level) = 38 mg/kg/day (males); 12 mg/kg/day (females).

LOEL (Low observed effect level) for systemic toxicity = 83 mg/kg/day in males; 46 mg/kg/day in females.

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

Data Evaluation Report

STUDY TYPE: Oncogenicity Study (83-2) - Mouse

MRID NO: 421732-01

TEST MATERIAL: Methanearsonic Acid

SYNONYMS: MAA

SPONSOR: Luxembourg Pamol, Inc.
5100 Poplar Ave.
Suite 2746
Memphis, TN 38137

TESTING FACILITY: Life Science Research Israel, Ltd.
PO Box 139,
Ness Ziona, 70 451 Israel

LAB STUDY NO.: LSRI Project Number PAL/023/MAA

TITLE OF REPORT: Methanearsonic Acid
Oncogenicity Study in the Mouse

AUTHORS: E. Gur, M. Pirak, T. Waner

REPORT ISSUED: July 8, 1991

CONCLUSIONS:

Methanearsonic acid was incorporated into the diet of 5 groups of 52 Charles River C3B6F1 mice per sex at concentrations of 0 (Control), 10, 50, 200 and 400 ppm for 104 weeks.

Mortality was not affected by treatment.

In the high and high-intermediate dose of both sexes, signs of toxicity were seen after 10-12 months of treatment. Loose and mucoid feces were seen at the high dose. A decrease in the mean body weight gain and an increase in water consumption occurred in the high dose of both sexes and the high-intermediate dose females. Food consumption was increased in the high dose females.

The colon, cecum and rectum showed a slight degree of diffuse cuboidal and squamous metaplasia in both sexes at the high dose versus the control.

Under conditions of this study, methanearsonic acid showed no evidence of carcinogenicity.

The Maximum Tolerated Dose (MTD) based on a decrease in the mean body weight gain = 400 ppm (82.8 mg/kg/day, HDT) - males; 200 ppm (46.4 mg/kg/day) - females.

NOEL = 200 ppm (37.5 mg/kg/day) - males; 50 ppm (11.5 mg/kg/day) - females.

LOEL (systemic toxicity) = 400 ppm (82.8 mg/kg/day) - males; 200 ppm (46.4 mg/kg/day) - females.

CLASSIFICATION: Core: guideline

The study satisfies the guideline requirement (83-2) for an oncogenicity study.

QUALITY ASSURANCE:

The final document had a signed quality assurance statement attesting to the fact that GLP guidelines were followed during the course of this study.

FLAGGING CRITERIA:

The final document had a signed statement noting that the EPA flagging criteria (40CFR 158.34) for potential adverse effects was applied and concluded that "this study neither meets nor exceeds any of the applicable criteria". The reviewer agrees with the final document's conclusion.

A. MATERIALS:

1. Test Compound

Chemical:	methanearsonic acid
Trade Name:	MAA
Label:	1) "Pamol Arad Ltd - Luxembourg Chemicals", (Consignment 1) 2) MAA 1 kg % AI 99.8% w/w; batch 107/84, 1/8/89 (Consignment 2).
Batch No.	107/84 in 2 consignments
Purity:	98.7 - 99.8% (Lab Analysis)
Description:	white crystals
Storage:	room temperature

a. Analyses of Formulated Diets:

The stability and homogeneity results noted below prove that the mixing technique produced a homogenous and stable mixture.

Stability

The week 1 diets were analyzed for stability on day 0 (all doses) and day 12 (low and high dose). The week 8 (low and high doses) diets were analyzed 12 days after preparation. The test material was within -7.5 to 9.5% of the required concentration during the 12 day periods.

Homogeneity

Homogeneity of MAA dispersal in the rodent diet was initially determined from the diet mix prepared on Weeks 1 and 8 of the study. The mixture was sampled from 6 different spots in the mixing vessel from each concentration and analyzed for MAA.

The percentage change from the theoretical value ranged from -13% at 10 ppm to -9% at 400 ppm.

Content Check

Checks were made to verify the test material content 11 times during the first 13 weeks and every 2 weeks, thereafter, until week 107. Samples were taken at each concentration level. The 10 ppm sample ranged from 6.0 to 11.2 ppm, the 50 ppm from 35 to 58 ppm, the 200 ppm from 155 to 236 ppm and the 400 ppm from 343 to 438 ppm.

2. Test Animals

Species:	Mice
Strain:	Charles River C3B6F1
Age:	3 weeks of age upon receipt
Weight:	Males 6.2 - 16.6 gm; females 8.7 - 16.1 gm on arrival (10% of the sample weighed)
Source:	Charles River Breeding Laboratories, Wilmington MA., USA.

B. STUDY DESIGN:

1. Animal Assignments

Animals were allocated to cages by a table of random numbers and housed singly. On commencement, all animals were weighed and any animal exceeding the mean value of the sex by 20% was replaced.

Fifty-two (52) animals per sex were assigned randomly to five (5) test groups and administered 0 ppm (group 1), 10 ppm (Group 2) 50 ppm (group 3), 200 ppm (Group 4) or 400 ppm (group 5) of the test material ad-mixed in the feed (Table 1).

Table 1

Animal Test Group Assignments[1]

Group	Treatment	Dietary Level[2] (ppm)	Animals on Test (M/F)
1	Control	0	52/52
2	MAA	10	52/52
3	MAA	50	52/52
4	MAA	200	52/52
5	MAA	400	51[3]/53

[1]Adapted from original report Vol I, p. 20.
[2]The dietary concentrations were expressed in terms of the material as supplied.
[3]After commencement of the study, animal No. 250 was found to be a female and discarded from the study.

2. Diet

Animals received the basal diet of Altromin 1321N chow (Altromin International Ltd., Lage, West Germany) and water ad libitum.

3. Diet preparation

Methanearsonic acid was incorporated into the powdered basal diet at the appropriate levels for the test diets each week. An initial premix was followed by dilution with further quantities of the diet and mixed. The dietary concentrations were expressed in terms of the material as supplied.

4. Water Supply

Drinking water was supplied to the cages via polyethylene bottles and stainless steel sipper-tubes. Water was taken from a water sterilizer connected to the public water supply and was routinely tested for physical, chemical and bacteriological characteristics.

5. Statistics

The significance of any intergroup differences in body weight performance, food consumption, water intake, absolute organ weight and hematology data was assessed as follows: homogeneity of variances was tested by the Bartlett's test. Where variances were homogeneous ($p>0.01$) then a parametric analysis of variance (ANOVA) was applied. When the F values were significant, Dunnett's multiple range test was applied for differences between control and treated groups. Where the variances were non-homogeneous the data was analyzed by the Kruskal-Wallis non-parametric ANOVA. If a significant difference between the groups was detected then the Dunn's test was applied for locating differences between the treated and control groups.

Survival function estimates were analyzed by the SAS Lifetest[tm] Procedure censoring for accidental deaths and scheduled sacrifice.

Organ weights were also analyzed using necropsy body weight as a covariant. Where a significant differences was found between the groups and this was at least partially accountable for by treatment ($p<0.05$), the multiple "t-tests" were applied for locating differences between the treated and controls.

Methods used in testing the significance of intergroup differences in pathology findings were described in Volume VI of the original report.

C. METHODS AND RESULTS:

1. Observations

Animals were observed daily for signs of ill health or toxic reaction to treatment. Animals were examined at least once weekly. Palpable swellings were identified as to location and described as to appearance, consistency and size.

2. Mortality

Mice killed in moribund condition, surviving to terminal sacrifice or dying during the course of the study were subjected to a gross necropsy. Moribund mice and those surviving until the end of the treatment period were killed by carbon dioxide inhalation.

Mortality was not affected by treatment. At commencement of terminal sacrifice, the survival rate among the males, in group order (beginning with the controls) were 87%, 87%, 90%, 83% and 92% and in the females 79%, 85%, 85%, 85% and 83%.

3. Clinical Signs

All treatment related observations were apparent starting from Week 40 until termination of the study.

Loose and mucoid feces were noted in both sexes of the high dose group. High and high-intermediate dose females showed an increased incidence of hypersensitivity to touch and tonic convulsions versus the lower doses and the controls. No change was noted in the male treated groups (Table 2).

Table 2

Principle Clinical Signs of Toxicity Throughout the Study[1]

	Group and Sex									
Observations[2,3]	1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
Feces loose	0	0	0	0	20	2	0	0	2	34
Feces mucoid	1	0	0	2	47	6	2	1	5	50
Hypersensitive	5	1	2	1	4	2	4	2	8	11
Tonic Convulsions	10	1	6	5	6	1	6	3	9	12

[1]Adapted from the original report Vol I p. 73 thru 86.
[2]Number of animals showing sign during the study.
[3]No statistical calculation performed.

4. Body Weight

Each animal was weighed on the first day of treatment, at weekly intervals for the first 13 weeks, bimonthly till Week 99 and weekly until termination of the study.

The mean body weight gain in high dose males was reduced by -17% when averaged throughout the study (Table 3). A decrease in the absolute body weight of the high dose males, as evidenced by a statistical difference from the control, was seen starting about week 45 and continued until termination.

In females, a reduction in the mean body weight gain of -18% and -46%, was noted in the high-intermediate and high dose levels, respectively, when averaged throughout the study (Table 3). A decrease in the absolute body weight of the high dose females, as evidenced by a statistical difference from the control, was seen starting about week 43 and continued until termination.

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Table 3

Mean Body Weight (gm) at Selected Intervals Throughout the Two Year Study[1]

	Group and Sex									
Week	1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
0	21	21	21	22	21	18	19	18	18	19
5	25	25	24	25	24	21	21	21	21	21
25	32	32	32	32	31	27	27	28	28	27
51	37	38	38	38	32[c]	35	35	34	33	29[c]
75	40	42	41	41	34[c]	38	38	38	36	30[c]
104	41	43	42	41	34[c]	40	39	38	36	31[c]
Change[d]	20	22	21	19	13	22	20	20	18	12
%[e]	--	10	5	-5	-35	--	-9	-9	-18	-46

[1]Adapted from original report, Vol I, p. 87 thru 93.
[c]significantly different from control, $p<0.001$.
[d]Change in weight from 0 week values. No statistical calculations performed.
[e]Percent difference compared to the control.

5. Food Consumption and Food Conversion Ratio

Food consumption was measured weekly for the first 13 weeks of treatment and biweekly, thereafter. The mean group intake was calculated at each time period.

In the female high dose level, food consumption increased 15.8% versus the control from week 47 until termination. Food consumption at the lower levels and in the males at all levels were considered to be not remarkable.

The food conversion ratio was considered to be not remarkable in both sexes throughout the course of the study.

6. Compound Consumption

Compound consumption expressed as mg/kg/day was calculated for each group/sex (Table 4).

Table 4

Mean Compound Consumption for Weeks 1-104[a,b,c]

Group	Males (mg/kg/day)	Females (mg/kg/day)
1	0.0	0.0
2	1.8	2.2
3	9.3	11.5
4	37.5	46.4
5	82.8	103.5

[a]Adapted from original report, Vol I, p. 101 thru 102.
[b]Calculated from the average food consumption and body weight at all time intervals during the study.
[c]Mean compound consumption calculated by the reviewer.

7. Water Intake

Water intake was measured weekly for the first 13 weeks of treatment and biweekly, thereafter, for all groups.

In the male high dosage group, water intake from week 45 until termination of the study was significantly increased ($p<0.001$). A similar pattern of water intake was apparent in the females. From week 41, an increased water intake was apparent in females of both the high and high-intermediate dose groups ($p<0.001$) until termination of the study. Compared to the respective controls, the high dose was 33% and 42% higher in the males and females, respectively and 17% higher in the high-intermediate females (Table 5).

Table 5

Mean Water Consumption (ml/animal/week) at Selected Intervals Throughout the Two Year Study[1]

	Group and Sex									
Week	1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
1	47	44	43[a]	43[a]	44	46	46	45	46	48
5	45	46	44	43	47	46	48	46	48	49
25	40	38	38[a]	38	39	39	42[a]	40	41	43[b]
45	37	36	36	39	53[c]	38	40	39	46[c]	61[c]
51	35	36	37	44[c]	59[c]	40	41	42	54[c]	64[c]
75	44	42	45	47[a]	71[c]	42	43	43	53[c]	75[c]
103	42	40	38	44	65[c]	45	47	46	52[c]	72[c]
Mean[d]	40	39	39	42	53	41	43	43	48	58
%[e]	--	-3	-3	5	33	--	5	5	17	42

[1]Adapted from original report, Vol I, p. 104 thru 110.
[a]significantly different from control, $p<0.05$.
[b]significantly different from control, $p<0.01$.
[c]significantly different from control, $p<0.001$.
[d]Mean of observations throughout study. No statistical calculations performed.
[e]Percent difference compared to the control.

8. Clinical Pathology

Blood was collected from the tail after 12, 18 and 23 months for differential white blood cell counts from groups 1 and 5 only. The following cell types were scored: neutrophils, lymphocytes, eosinophils, monocytes and normocytes.

The differential counts were not remarkable throughout the course of the study.

9. Sacrifice and Pathology

Animals in extremis and those that completed their scheduled test period were sacrificed by carbon dioxide inhalation.

The study was terminated after 104 weeks of treatment. Terminal sacrifice was undertaken during weeks 105-108. Animals continued to receive the treated diet until necropsy.

All animals that died or were scheduled for sacrifice were subject to gross and pathological examination. The checked (X) tissues were collected for gross and histological examinations from the control (Group 1) and high (group 5) dose groups. Organs and tissues denoted by an (^^) were examined in Groups 2, 3 and 4. The (XX) organs were weighed. Organs and tissues marked with a (*) were required by the 83-2 guidelines.

Organs and Tissues Examined Histopathologically at the Terminal Sacrifice

Digestive	Cardiovas./ Hematology	Neurologic
	X aorta*	XX brain*
X esophagus*	XX heart*	
X stomach*^^(d)	X bone marrow*(e)	X spinal cord (3 levels)
X duodenum*^^	X lymph nodes*	X sciatic nerve^^(c)
X jejunum*	cervical/mesen	X pituitary*
	/abdominal	X eyes* & optic nerve*
X ileum*	XX spleen*(c)	Glandular
X cecum*^^	X thymus*	X adrenals*^^
X colon*^^	Urogenital	X parathyroids*^^
X rectum*^^	XX kidney*^^	X thyroids*^^
XX liver*^^	X urinary bladder	Other
X pancreas*	XX testes*(a)	X bone*(e)
Respiratory	X prostate*	X skeletal muscle*
X trachea*	X seminal ves.	X skin*
XX lung*^^	X ovaries*	X gall bladder*
	X uterus*(b)	X Harderian gland
		X salivary gland*
		X abnormalities^^*
		X skull (nasal passages)

X Groups 1 and 5 examined microscopically
XX weighed and examined microscopically.
^^ microscopic examination from Groups 2, 3 and 4.
* specified by the guidelines
(a) with L and R epididymides and seminal vesicles
(b) corpus and cervix, (c) males only, (d) fundus, pylorus
(e) sternum including marrow, tibia femoral joint

a. Organ Weights

Organ weights were excluded from calculations where the organ had a visible mass or other abnormality at necropsy. Similarly, outlying values were also excluded.

No significant differences in the absolute organ weights were apparent at necropsy.

When the spleen was analyzed using the body weight as the covariant, differences were noted in the spleen and liver. The spleen in the female high and high-intermediate doses were lighter than the controls. The difference was mainly attributed to treatment (Table 6).

Table 6

Spleen Weight Using Body Weight As A Covariant
Least Square Means[1]

Group/ Males	LSMean[2] (gm)	Group/ Females	LSMean[2] (gm)
1	0.10	1	0.22
2	0.09	2	0.18
3	0.09	3	0.21
4	0.08	4	0.15[b]
5	0.07	5	0.15[a]

[1]Adapted from original report, Vol I, p. 116-117.
[2]LS = least square mean (measured in gm)
[a]significantly different from control, $p<0.05$.
[b]significantly different from control, $p<0.01$.

b. Pathology Findings

1. Gross Pathology Findings:

A slight increased incidence of abnormal cecal contents was noted among high dose level animals (Table 7).

Table 7

Incidence of Abnormal Cecal Contents Related to Treatment with Methanearsonic Acid[a,b]

	Group and Sex									
	1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
Animals Examined	52	52	52	52	51	52	52	52	52	52
CECUM contents:										
mucoid, foamy, fluid or soft	0	0	0	0	4	2	0	1	4	12

[a]Adapted from the original report p. 36.
[b]No statistical evaluation performed.

2. Microscopic Pathology

Digestive Tract

Changes considered related to treatment were noted in the rectum, colon and cecum. Other lesions possibly related to treatment were seen in the kidney and adrenal glands.

The large intestine of both male and female high dosage animals showed a lesion consisting of diffuse, slight cuboidal to squamous metaplasia of the surface epithelial columnar absorptive cells (Table 8).

Table 8

Lesions of the Digestive Tract Related to Treatment with Methanearsonic Acid[1]

	Group and Sex									
	1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
CECUM - No. examined	49	52	49	50	49	47	50	48	52	52
Epithelial columnar absorptive cells to cuboidal to squamous metaplasia: D,S.	0	0	0	0	29[c]	0	0	0	0	35[c]
%[2]	-	0	0	0	59	-	0	0	0	67
COLON - No. examined	51	52	51	50	49	49	50	49	51	52
Epithelial columnar absorptive cells to cuboidal to squamous metaplasia: D,S.	0	0	0	0	14[c]	0	0	0	0	17[c]
%[2]	-	0	0	0	29	-	0	0	0	33
RECTUM - No. examined	50	52	51	52	49	50	50	51	51	52
Epithelial columnar absorptive cells to cuboidal/squamous metaplasia: D,.S.	0	0	0	0	39[c]	0	0	0	0	42[c]
%[2]	-	0	0	0	80	-	0	0	0	81

[1]Adapted from the original report p. 41.
[2] % = Lesion/number of animals.
[c]significantly different from control, $p<0.001$.
D = diffuse, S = slight

Kidney

Two changes, progressive glomerulonephropathy in males ($p<0.001$) and nephrocalcinosis in males ($p<0.001$) and females ($p<0.01$) showed a positive, significant trend which was considered as possibly related to treatment (Table 9).

Table 9

Lesions of the Kidney Possibly Related to Treatment with Methanearsonic Acid[1]

	Group and Sex									
	1M	2M	3M	4M	5M	1F	2F	3F	4F	5F
No. of kidneys exam.	52	52	52	52	51	52	52	52	52	52
Progressive glomerulonephropathy:										
slight, subchronic	25	27[c]	38[c]	39[c]	46[c]	7	5	10	3	3
moderate, subchronic	0	0	1	1	0	1	0	0	1	0
slight, chronic	0	0	0	0	0	1	0	0	0	0
%	48	52	75	77	90	17	10	19	8	6
Nephrocalcinosis:										
slight, focal	25	30[c]	30[c]	45[c]	45[c]	0	1[b]	1[b]	2[b]	5[b]
%	48	58	58	87	88	0	2	2	4	10

[1]Adapted from the original report p. 42.
[b]positive significant trend $p<0.01$.
[c]positive significant trend $p<0.001$.

DISCUSSION:

No treatment related mortality occurred.

Signs of toxicity started at approximately 10-12 months after commencement of treatment in the high dose males and the high and high-intermediate dose females as evidenced by clinical signs, decreased rate of weight gain, increased water and decreased food consumption as noted below.

Clinical signs observed in both sexes at the high dose level versus the respective controls were loose and mucoid feces while high and high-intermediate dose females showed an increased incidence of hypersensitivity to touch and tonic convulsions versus the lower doses and the controls (Tables 2).

A decrease in the mean body weight gain occurred throughout the study in both sexes when compared to the controls. In the high dose males, a decrease of -35% was noted while in the high-intermediate

and high dose females a reduction of -18% and -46% was seen, respectively. A decrease in the absolute mean weight body weight occurred starting at week 45 in the high dose males and week 43 in the high dose females which continued until termination (Table 3). High dose level females also showed a decrease in food consumption of 16% starting on week 47 and continuing until termination.

After approximately 10-12 months of treatment, the mean water intake was also increased throughout the study in the females of the high-intermediate and high dose groups and males at the high dose level (Table 5).

The absolute organ weight of the spleen versus the controls were not remarkable. Analysis using body weight as the covariant indicated a treatment related decrease in the spleen weight at the high and high-intermediate dose level. This finding was not supported by any macroscopic or microscopic effect and was not dose related. The biological significance of this finding was unknown (Table 6).

Pathology changes were observed in the rectum, colon and cecum of both sexes. The changes were considered to be slight and were characterized by conversion of the normal absorptive columnar epithelium to diffuse cuboidal to squamous metaplasia (Table 8).

Epithelial metaplasia is usually associated with chronic irritation or endocrine imbalance and can be presented as substitution of a columnar mucous-secreting surface by a stratified squamous epithelial surface. Metaplasia can usually be considered an adaptive response of an epithelium and its significance can range from a simple adaptive response to a pre-neoplastic change. No neoplastic changes related to treatment with the test substance were noted in the large intestine.

In the kidney, two changes, progressive glomerulonephropathy in males and nephrocalcinosis in males and females showed a positive significant trend. These lesions were consistent with the normal spectrum of spontaneous renal lesions encounter in aged B6C3F1 mice and no difference in the character and/or severity of lesions were noted between groups. These lesions, were considered to be possibly related to the administration of the test material (Table 9).

CONCLUSIONS:

Methanearsonic acid was incorporated into the diet of 5 groups of 52 Charles River C3B6F1 mice per sex at concentrations of 0 (Control), 10, 50, 200 and 400 ppm for 104 weeks.

Mortality was not affected by treatment.

In the high and high-intermediate dose of both sexes, signs of toxicity were seen after 10-12 months of treatment. Loose and

mucoid feces were seen at the high dose. A decrease in the mean body weight gain and an increase in water consumption occurred in the high dose of both sexes and the high-intermediate dose females. Food consumption was increased in the high dose females.

The colon, cecum and rectum showed a slight degree of diffuse cuboidal and squamous metaplasia in both sexes at the high dose versus the control.

Under conditions of this study, methanearsonic acid showed no evidence of carcinogenicity.

The Maximum Tolerated Dose (MTD) based on a decrease in the mean body weight gain = 400 ppm (82.8 mg/kg/day, HDT) - males; 200 ppm (46.4 mg/kg/day) - females.

NOEL = 200 ppm (37.5 mg/kg/day) - males; 50 ppm (11.5 mg/kg/day) - females.

LOEL (systemic toxicity) = 400 ppm (82.8 mg/kg/day) - males; 200 ppm (46.4 mg/kg/day) - females.