DATA CALL IN TRACKING & TRANSMITTAL SHEET
FOR RESPONSES TO NOTICES

4/15/88

NOTE: PLEASE KEEP THIS TRANSMITTAL SHEET WITH ALL DATA ENCLOSED.

TRANSMITTED TO: Product Manager-23; Special Review Br.; Toxicology Br.

CHEMICAL MSMA / DSMA & MAA

Specialist's name Geri Werdig

IDENTIFICATION OF PRODUCT

Date of notice 9/26/83

Date response(s) ~~received~~ due 7/91

Registration No(s) _____ _____

_____ _____

_____ _____

_____ _____

Company Name Pamol for MAA Task Force

Date processing began _____

☐ FORMULATION OR END-USE PRODUCT

Date granted & relayed to PM _____

Source Reg. No. _____

☐ VOLUNTARY CANCELLATION

Date relayed to PM or Branch Chief _____

☐ SUSPENSION

Date issued _____

Effective date _____

☐ OCM STOP SALE, USE, OR REMOVAL ORDER

Date Issued _____

☒ OTHER

Comments This is the 1st indication of possible adverse effects from methane arsonates (MAA) in rats. We will keep you informed as added information is submitted.

THIS TRANSMITTAL CONTAINS CONFIDENTIAL BUSINESS INFORMATION ☐ yes ☒ no

To Sue put in MSMA & MAA cswell file

BEST AVAILABLE COPY

Geraldine Werdig
Chief, Data Call In Program

Tof
4/15

Tel-Aviv, March 29, 1988
247/PAM-Var-E

Ms. Geraldine Werdig
Data Call-In Program
Registration Division (TS-767C)
Office of Pesticide Programs
U.S. Environmental Protection Agency
Crystal Mall No. 2
1921 Jefferson Davis Highway
Arlington, VA 22202
U.S.A.

cc: Dr. G. Eilrich - Fermenta
Mr. P. Bomar - Inter-Ag
Dr. A. Schwerdtle - Vineland
Mr. S. Friedman - Luxembourg Pamol Inc.

Dear Ms. Werdig,

Subject:
- Special Report
- MAA Oncogenicity Studies in Rats
- Report Submitted on behalf of MAA Task Force

The letter and data from Life Science Research Israel of March 27, 1988 enclosed herewith, were just received in our office.

In this letter, there is reference to histopathological lesions observed in association with the MAA chronic oncogenicity study in rats. The significance and meaning of these findings are not yet defined at this stage as the lab performing the study has not yet finished its research. In addition, these are preliminary results which have not gone through quality assurance procedure and the lab has not drawn conclusions except that the high dose level far exceeded the maximum tolerated dose (MTD) for rats so that the effects seen at the high dose level were related to the excessive dose received by the animals. Nevertheless, we have decided to alert the EPA to these effects as they may be related to FIFRA Section 6(A) (2) reporting requirements.

As we shall receive more conclusive information regarding these and other findings, we shall not fail to inform you.

On behalf of the MAA Task Force, we remain,

Sincerely yours,
PAMOL LIMITED ARAD

E. Koren, Ph.D.,

EK/ls

ENCL:

Life Science
Research Israel Ltd.

P.O. Box 139
Ness Ziona 70451, Israel
Tel: (08) 472599, 472777
Tlx: 381368. Fax: (8) 471137

27th March, 1988

Dr. E. Koren,
Pamol Ltd.,
P.O. Box 13,
Tel Aviv,
Israel.

Dear Dr. Koren,

Please find enclosed a summary of histopathology lesions associated with treatment with methanearsonic acid (MAA). These lesions were observed in Fischer F344 rats treated via the diet for two years.

Dosages used were as follows: 0, 50, 400 1300 ppm in the control, low, intermediate and high dosage groups, respectively. In Week 53 the high dose was reduced to 1000 ppm and again another reduction to 800 ppm was carried out in Week 60. The necessity of reducing the dose level twice was due to excess mortality. This was carried out folllowing the advice of Dr. W. Burnham of the EPA and is indicative that the maximum tolerated dose (MTD) for rats was exceed at the high dose level.

Sincerely yours,

A. Nyska, D.V.M
Head, Pathology Department

Z. Paster, Ph.D.
Managing Director

Histopathological Findings

Toxic and carcinogenic response due to MAA treatment were dose-related and limited to the intermediate and high dosage groups.

A. Organs affected primarily or secondarily by MAA during the inital 59 weeks of treatment were:

1. Non-neoplastic lesions

Reduction of the Abdominal fat pads associated with serous atrophy of fat pads, acute or subchronic peritonitis.

Caecal, colonic and rectal inflammation; cuboidal to squamous metaplasia of the epithelial absorptive cell, mucosal ulceration, post perforating ulceration, regenerative hyperplasia, mucosal congestion, mucosal covering layer composed of mucous secretion and exfoliated cells, dysplasia of the epithelial intestinal glands, increased presence of goblet cells in the intestinal glands.

Duodenal inflammation, ulceration, regenerative hyperplasia.

Ileal inflammation and cuboidal to squamous metaplasia of the epithelial absorptive cells.

Jejunual inflammation.

Pancreatic acute or subchronic inflammation.

Gastric mucosal vascular congestion.

Thyroidal higher lining follicular epithelium.

Uterine, testicular, prostatic and seminal vesicles - acute or subchronic inflammation.

Bone marrow reduction in cellularity.

Splenic reduction of lymphocytes from white pulp.

Thymic - relatively earlier appearance of the normaily age-associated atrophy.

Renal - basophilic tubules, pyelonephritis, cortical tubular cystic dilatation, papillary necrosis.

Urinary bladder - epithelial transitional cell hyperplasia, cystitis and increased incidence of luminal distension.

Ureter - inflammation and presence of plug.

Parathyroids - hyperplasia.

2. Neoplastic lesions

Caecal, colonic, rectal adenocarcinomas were observed only in males of the high dosage group. (see text table No.1)

B. Histopathological findings in Weeks 60-108 (including terminal kill period)

1. Non-neoplastic lesions

Abdominal wall and cavity - acute or subchronic peritonitis, serous atrophy of the abdominal fat pads.

Caecum, colon, rectum - the same range of lesions as described in rats dying during Weeks 1-59.

Duodenum - inflammation, ulceration, regenerative hyperplasia.

Ileum, jejunum - cuboidal to squamous metaplasia of the cell absorptive columnar epithelium, mucosal covering layer composed of mucous secretion containing exfoliated cells.

Pancreas - acute or subchronic inflammation.

Stomach - glandular mucosal congestion.

Thyroids - increased height of the lining follicular epithelium.

Spleen - depletion of lymphocytes.

Thymus - earlier appearance of the normally age-associated atrophy.

Bone marrow - reduced cellularity.

Testes, seminal vesicle, prostate and uterus - inflammation and atrophy (uterus).

Kidneys - hydronephrosis, pyelonephritis and papillary necrosis.

Urinary bladder - transitional cell hyperplasia.

Ureter - luminal distension, inflammation and transitional cell hyperplasia.

2. Neoplastic lesions

Caecum, colon, rectum - relatively high incidence of adenocarcinomas were observed in the high dosage groups. Sporadic cases of leiomyomas and leiomyosarcomas were observed in the caecum and rectum in the high dosage group (see text table No.1).

Parathyroids - increased incidence of adenomas were observed in the intermediate and high dosage groups (see text table No.1).

TEXT TABLE NO. 1

Incidence of neoplasms in the large intestinal and parathyroid - total and divided per periods of death

Group	Weeks 1-52								Weeks 53-59							
Animals examined	1M 2	2M 1	3M 0	4M 14	1F 1	2F 1	3F 0	4F 6	1M 0	2M 0	3M 0	4M 11	1F 0	2F 0	3F 0	4F 2
Neoplasms																
CAECUM																
Adenocarcinoma Grade B	0	0	0	2												
COLON																
Adenocarcinoma Grade B									0	0	0	1				
Adenocarcinoma Grade D									0	0	0	1				
RECTUM																
Adenocarcinoma Grade B	0	0	0	3					0	0	0	4				

TEXT TABLE NO. 1 - continued

Incidence of neoplasms in the large intestinal and parathyroid - total and divided per periods of death

Group	Weeks 60-104								Weeks 104-108							
	1M	2M	3M	4M	1F	2F	3F	4F	1M	2M	3M	4M	1F	2F	3F	4F
Animals examined	23	29	27	15	11	19	13	13	35	30	33	20	48	40	47	39
Neoplasms																
CAECUM																
Adenocarcinoma Grade B	0	0	0	4	0	0	0	1	0	0	0	4				
Adenocarcinoma Grade D									0	0	0	1				
Leiomyoma													0	0	0	1
COLON																
Adenocarcinoma Grade B					0	0	0	1								
Adenocarcinoma Grade D									0	1*	0	0				
RECTUM																
Adenocarcinoma Grade B	0	0	0	8	0	0	0	4	0	0	0	12	0	0	0	22
Adenocarcinoma Grade C													0	0	0	1
Leiomyosarcoma	0	0	0	1	0	0	0	1								
PARATHYROID																
Adenoma	0	0	2	2	0	0	0	2	1	0	2	2	0	0	0	2

*For comment, see following page

* In a single male rat of the low dosage group (2M 79) a case of adenocarcinoma grade D was observed. The tumour is regarded as spontaneous and unrelated to treatment for the following rationale. This tumour differs in its morphology from those neoplasms seen in the large intestine and induced by MAA. The mass is large, extensive and infiltrating more than those induced by MAA. The tumour is of mucinous adenocarcinoma type (excessive mucin production associated with the formation of lakes of mucin). Characteristically, in the present case (2M 79) there is excessive stromal proliferation with the formation of cartilage and bony spicules. Such morphological variant was not seen in any other rat treated by MAA.

TEXT TABLE NO. 1 - continued

Incidence of neoplasms in the large intestinal and parathyroid - total and divided per periods of death

Group	Total							
Animals examined	1M 60	2M 60	3M 60	4M 60	1F 60	2F 60	3F 60	4F 60
Neoplasms								
CAECUM								
Adenocarcinoma Grade B	0	0	0	10	0	0	0	1
Adenocarcinoma Grade D	0	0	0	1				
Leiomyoma					0	0	0	1
COLON								
Adenocarcinoma Grade B	0	0	0	1	0	0	0	1
Adenocarcinoma Grade D	0	1*	0	1				
RECTUM								
Adenocarcinoma Grade B	0	0	0	27	0	0	0	26
Adenocarcinoma Grade C					0	0	0	1
Leiomyosarcoma	0	0	0	1	0	0	0	1
PARATHYROID								
Adenoma	1	0	4	4	0	0	0	4

* See comment on previous page