



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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM MAY 26 1982

TO: Richard Mountfort (23)
Registration Division (TS-767)

SUBJECT: Methanearsonates; EPAA Reg.#677-267; Miscellaneous
Data; Company Response to Toxicology Branch Questions
CASWELL#549A Accession#247264, -265

Recommendation:

1) Methane arsonic acid (MAA) is unquestionably oncogenic to the thyroid of male rats. This fact is evident by statistical analysis of the thyroid tumors using Fisher's Exact Test of the high-dose males (13/68) to the control males (4/66) which yields a $p = 0.021$. Additionally, statistical analysis using Fisher's Exact Test of the follicular tumors (adenomas and carcinomas combined) of male rats at the high-dose (6/68) to all other male rats in the study which includes the control males plus the male rats at 25, 50 and 100 ppm groups (0/236) yields a $p = 0.000$. Both types of statistical analyses demonstrate that MAA is oncogenic. This finding triggers an oncogenic RPAR criterion. However, the registrant has submitted applicator exposure data. The applicator exposure data and the dietary exposure data will be used together with the results of the 2-year rat study to provide a basis for a risk assessment.

Review:

A. These data below were previously reviewed in memo of 6/10/81 from W. Dykstra to R. Mountfort.

1) Two-Year Chronic Feeding Study of Methane arsonic acid in Rats; thyroid histopathology; W.D. Rapp, D.V.M.; 12/4/80

Summary - Thyroid Histopathology

Dose (ppm)	MALES					FEMALES				
	0	25	50	100	200	0	25	50	100	200
Group Identification:	1	2	3	4	5	6	7	8	9	10
Initial Group Size:	75	75	75	75	75	75	75	75	75	75

Histologic Change
or other status:

Not evaluated-										
Not submitted	2	17	8	17	4	8	28	32	35	2
Tissue not in section	5	3	3	1	3	11	7	1	4	1
Tissue section incomplete	2	0	4	2	0	1	0	1	3	0
Autolysis (a)	24	29	32	32	21	9	17	20	14	28
Not remarkable (b)	36	24	22	21	30	42	21	13	15	37
cyst	0	0	0	0	0	0	0	1	0	0
cyst, colloid	2	0	0	0	0	0	0	0	0	1
cyst, ultimobranchial-duct	0	0	0	0	0	0	0	0	1	0
subacute thyroiditis, focal										
minimal	0	0	1	0	0	0	0	0	0	0
moderate	0	0	0	0	1	0	0	0	0	0
hyperplasia, follicular										
diffuse	0	0	0	0	0	0	0	1	0	0
focal	0	0	0	0	2	0	0	0	0	1
hyperplasia, medullary cell										
focal	0	0	0	0	1		0	0	0	0
adenoma, follicular	0	0	0	0	4*	1	1	0	0	2
adenoma, papillary	2	0	2	1	1	0	1	0	0	2
adenoma, medullary cell	2	2	2	1	4	2	0	2	1	1
carcinoma, follicular	0	0	0	0	2*	1	0	3	1	0
carcinoma, papillary	0	0	1	0	1	0	0	0	1	0
carcinoma, medullary cell	0	0	0	0	1	0	0	1	0	0

(a) Degree of change sufficient to preclude detailed histomorphologic evaluation, but generally suitable for determination of hyperplasia and neoplasia and included herein.

(b) Within normal histologic limits.

*A statistical analysis by Dr. Berrettoni was performed on Follicular adenomas and carcinomas (see pages 3 and 4).

2) Conclusions of Dr. Rapp regarding the study.

Thyroid glands from rats of the two-year study of methane arsonic acid were evaluated for histomorphologic change. Tissue from 573 rats of the initial 750 animals were available for examination. Neoplastic and hyperplastic changes of the thyroid were present with slightly greater total incidence in male animals, and with some general prominence related to Group 5 males and Group 8 females. The comparison of the total incidence for all thyroid neoplasms by group and sex, and of the incidence of each histologic classifications was not considered to define an oncogenic effect of the test-substance. Other histomorphologic changes of the thyroid represented the sporadic occurrence of spontaneous lesions.

3) Toxicology Branch conclusions regarding the study.

The pathological report submitted has been statistically analyzed using Fisher's Exact Test. Comparison of thyroid tumors out of 66 thyroids evaluated in the control male rats (0 ppm) to 13 thyroid tumors out of 68 thyroids evaluated in the high-dose male rats (200 ppm) yielded a p value of .021 which is statistically significant. Toxicology Branch concludes that methane arsonic acid is oncogenic to the thyroid of male rats at 200 ppm.

4) Statistical Evaluation of 2-Year Chronic Feeding Study of Methane Arsonic Acid in Rats - Thyroid Histopathology;
J.V. Berrettoni, Ph.D; 3/15/81

FOLLICULAR ADENOMA AND FOLLICULAR CARCINOMA
 STATISTICAL ANALYSIS AND CONCLUSIONS

Dosage Level Groups	Control 1	MALES Dosages				Control 6	FEMALES Dosages			
		2	3	4	5		7	8	9	10
Sample Sizes	66	55	60	55	68	55	40	41	33	72
Number of Follicular Adenoma Occurrences	0	0	0	0	4	1	1	0	0	2
Number of Follicular Carcinoma Occurrences	0	0	0	0	2	1	0	3	1	0
Total	0	0	0	0	6	2	1	3	1	2

5) Statistical Conclusions by Dr. Berrettoni

1. No statistical difference exists between dosage levels of males vs. male control and similarly with females vs. female control for both Follicular Adenoma and Follicular Carcinoma.
2. The same conclusion applies to the sum of occurrences of Follicular Adenoma and Follicular Carcinoma.
- 3.(a) Statistically there is no difference in occurrences in dosage levels over males and females over Follicular Adenoma and Follicular Carcinoma. This says that there is a single population with an expected percent of 3.07 occurrences (13/424).
(b) Also there is no statistical significance between the 3.07% at dosage levels and the control at 1.65% (2/121).

6) Toxicology Branch conclusions regarding the follicular tumors.

A comparison of the follicular tumors in high-dose males to all other males in the study which includes the control males plus the male rats at 25, 50 and 100 ppm groups is 6/68 (high-dose) to 0/236 (all other males) using Fisher's Exact Test for statistical analysis yields a $p = 0.000$ which is very highly significant.

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Toxicology Branch
Hazard Evaluation Division (TS-769)

5/13/82

WJD
5/15/82

Thyroid Tumors

ppm	#	ELSP	Total	$\bar{x} \pm 2(S.D.)$	One tail P Statistic Fisher's
0.000	4	66		0.00 \pm -(0.51)	
200.000	13	36		19.12 \pm -(10.00)	0.021

