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

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

April 6, 1983 APR 18 1983

TO: Mr. Donald Stubbs, PM 41
Process Coordination Branch
Registration Division (TS-767)

SUBJECT: 83-LA-04, Section 18 request for use of Monosodium Methanearsonate (MSMA) ~~on~~ sugar cane
CASWELL NOS. 582, 549A

Based on Mr. Litt's memo of March 14, 1983 there is a certain oncogenic risk associated with methane arsonic acid ingestion that, because of limitations in the conduct of the study, are difficult to qualify with confidence. The upper 95% bound on existing risks from the TMRC (cottonseed and citrus) are estimated at 5×10^{-5} based on the most conservative one-hit model. If a use-adjusted TMRC is used, the upper 95% bound on the risks are 1.9×10^{-6}. However, the experimetal data are so fragmentary that these estimates may be modified if a new and better study becomes available.

Somewhat similar estimates can be made for the proposed Section 18 on sugar cane. The daily exposure would be 2.73×10^{-3} mg/kg/day corresponding to a life-time risk of 3.7×10^{-4}. If we assume that this Section 18 (and resulting exposure) is only for one year, the one year risk would be 1/70 of 3.7×10^{-4} or 5.3×10^{-6}. This risk of 5.3×10^{-6} is based on 100% of the crop treated and is the only assumption that can be made at this time. When the risks of the current use-adjusted TMRC are compared to the incremental increase from one-year of the Section 18, the requested Section 18 represents a 270% increase in the existing risk from the dietary exposure alone.

No exposure values or risk assessments have been considered for applicators at this time.

William L. Burnam, Acting Chief
Toxicology Branch
Hazard Evaluation Division (TS-769)

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

MAR 31 1983

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: 83-LA-04. Section 18 request for use of monosodium methanearsonate (MSMA) on sugarcane.

FROM: Richard Loranger, Chemist, Residue Chemistry Branch, Hazard Evaluation Division (TS-769) R. Loranger

THRU: Charles L. Trichilo, Chief, Residue Chemistry Branch Hazard Evaluation Division (TS-769)

TO: D. Stubbs, PM41, Process Coordination Branch, Registration Division (TS-767)

and

Toxicology Branch, Hazard Evaluation Division (TS-769)

The Louisiana Department of Agriculture requests an emergency exemption for the use of MSMA (monosodium methanearsonate) to control itchgrass and johnsongrass in sugarcane.

Temporary tolerances were established for residues of methanearsonic acid (from application of its monosodium salt) at levels of 1.5 ppm (expressed as As_2O_3) in sugarcane and 3 ppm for its byproducts molasses, sugar and syrup in conjunction with PP#3G1357 (7/29/76, Federal Register). Presumably these tolerances have since expired.

The proposed use of MSMA is application of 2.5-4 lb ai/A in spring (Mar-Apr.) as a directed spray or over-the-top application (latter for stubble cane only). If necessary retreatment will occur 3-4 weeks later but not after June 1. Only two applications are to be made per growing season. This is essentially the same use requested in PP#3G1357 (2.5-5 lb ai/A) although the latter had restrictions against feeding and grazing of treated foliage. Such limitations should be added to this emergency use to ensure no detectable residues result in meat and milk.

Methanearsonic acid (MAA) is rapidly absorbed and translocated by johnsongrass and cotton (^{14}C studies, see PP#9F0794). The methanol extracts of the grass contained sugar and organic acid (incl. amino acid) complexes of MAA. A study with bean plants found a ninhydrin positive complex of MSMA. There was no evidence of demethylation to form inorganic arsenicals nor of reduction to trivalent arsenic compounds (Weed Science, 19, 558 (1971)). In any case the analytical method determines total As including bound residues as well as pentavalent and trivalent arsenic.

Total arsenic is measured spectrophotometrically via the red complex formed between arsine and silver diethyldithiocarbamate. The arsine is generated by digestion of the sample with nitric and sulfuric acids followed by reduction of the arsenic acid with zinc and HCl. Control values were 0.01-0.07 ppm As_2O_3 in sugarcane juice and 0.03-0.37 ppm in bagasse (A. Smith, May 8, 1974, PP#3F1357). No recovery data were required since this is the official AOAC method for total arsenic.

Residue data in the aforementioned petition reflect the proposed use. Following 1-2 applications of 2-4 lb ai/A, methanearsonic acid residues (expressed as As_2O_3) in whole sugarcane were <0.01-1.40 ppm. Cane having 0.03-0.49 ppm residues was processed and concentration factors of 1.4 X and 1.8X observed for syrup and sugar, respectively (A. Smith, May 3, 1976 PP# 3G1357). Based on these data we recommended temporary tolerances of 1.5 ppm (as As_2O_3) for sugarcane and 3 ppm for the byproducts bagasse, sugar, molasses and syrup. The same levels are appropriate for this emergency exemption.

Sugarcane molasses may comprise up to 20% of the diet for beef cattle and 10% for dairy cattle, swine, horses and lambs. Bagasse is also fed to cattle as a minor dietary constituent (5%). Therefore, as much as 0.75 ppm MAA (as As_2O_3) could appear in the diet for beef cattle (25% X 3 ppm). Since feeding 4.25 ppm MAA to cattle for 9 weeks resulted in no residues above normal background levels (<0.003-0.02 ppm as As) in milk and tissues (E. Gunderson, May 26, 1969, PP#9F0974), we conclude the proposed use falls under Category 3 of Section 180.6(a). A poultry feeding study using MAA levels of 0.042, 0.42, 4.25 ppm (expressed as As_2O_3) showed no residues in tissues or eggs except for 0.07 ppm average As in eggs at the highest level. Since the expected poultry exposure is only about 0.12 ppm (4% of diet X 3 ppm), we conclude no detectable residues are expected in poultry or eggs from this emergency use. These conclusions are contingent upon a restriction against the grazing or feeding of treated foliage as noted above.

Conclusions and Recommendation

1. Residues of methanearsonic acid (expressed as As_2O_3) in or on sugarcane and its byproducts (bagasse, sugar, molasses, syrup) from the proposed use will not exceed 1.5 ppm and 3 ppm, respectively.

2. Provided a restriction is added to the Section 18 label prohibiting the grazing and feeding of treated foliage to livestock, no detectable residues are expected in meat, milk, poultry and eggs.

TOX considerations permitting, we have no objections to this emergency exemption if the label is amended as noted in Conclusion 2. An agreement is needed with FDA regarding the legal status of treated sugarcane in commerce.

Burnam

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

MAR 14 1983

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

TO: Richard F. Mountfort
PM Team 23
Registration Division (TS-767)

THRU: Orville E. Paynter, Ph.D.
Toxicology Branch, HED (TS-769)

WEB/Burnam for OEP 3.11.83

THRU: John W. Melone, Director
Hazard Evaluation Division (TS-769)

SUBJECT: Methane Arsonic Acid, Risk Assessment for Carcinogenicity

Background

The WARF Institute 2-Year Chronic Feeding Study of Methane Arsonic Acid (MAA) in rats provides the data (see Table 1 attached) used for the low-dose risk-extrapolation process of the quantitative risk assessment requested by RD. The data displayed in Table 1* have been reviewed with the branch pathologist, Dr. L. Kasza, who recommended that follicular and para-follicular tumors be analyzed separately, as shown on the bottom of Table 1. Dr. Kasza has also confirmed that only animals with definite diagnosis of not remarkable or with specific findings be included in that denominator defining the animals at risk in each group.

Limitations of the Study Data

1. The data from the 25, 50, and 100 ppm groups are too sparse to contribute to meaningful inference because 2/3 of the animals entered into study do not have a definite thyroid pathology report. In fact, the number of animals with autolyzed thyroid tissues exceeds the number with useful diagnosis in each of these three groups, see Table 1. In addition to the possibility of bias arising from autolysis

* Table 1 has been adapted from a summary Table included in the registrant's summary of the study.

Table 1 demonstrates that 20-27% of these animals had thyroids which were not examined microscopically. While it may be that the study protocol required complete examination of only the control and high-dose animals, common sense and/or scientific judgment should have dictated an implied need to examine all thyroid tissues once it became evident that a potential biological effect or a statistically significant increase over control was noted in the high-dose group.

2. The data available for analysis in the control and high-dose males is also subject to considerable bias resulting from both lack of data and reported autolysis:

	Control Males	High Dose Males
Initial Group	75	75
Not Evaluated or Autolyzed	33	28
Total Classified	42	47
Not Remarkable	36	30
Thyroid Effect	6	17
(Follicular Tumor)	(2)	(8)
(Para-Follicular Tumor)	(2)	(5)

As shown in the above Table, the observed or reported incidence of thyroid follicular tumors is 2/42 (4.76%) in male controls and 8/47 (17.02%) in high-dose males. If all those control rats which were not evaluated were positive for this follicular tumor and all unevaluated high-dose males negative, the incidence may be 35/75 (46.66%) in controls vs. 8/75 (10.66%) in the high-dose males. At the other extreme i.e., all unevaluted control rats were negative and all unevaluated high-dose rats positive, the incidence may be 2/75 (2.66%) in controls vs. 36/75 (48%) in the high-dose group.

3. Another potential source of bias is the lack of litter identification. The litter effect should be determined because the study animals were the F_1 generation of parents randomized to study. It is generally agreed that the genetic similarity among litter-mates may result in more uniform response to chemical stimulae than typically found for the animal strain. As a result of this expectation less weight should be placed on 8 tumor-bearing animals distributed among 2-3 litters than would be the case if the 8 tumor-bearing animals were distributed in 5-8 litters.

Estimates of Human Exposure to MAA

1. Based on published tolerances of 0.700 ppm for cottonseed (oil) and 0.350 ppm for citrus fruit we find that if the food factors 0.15% of the diet for cottonseed and 3.81% for citrus are used directly, the TMRC estimated daily dietary exposure is 3.6×10^{-4} mg/kg/day. This is the maximum estimate of dietary exposure.

2. If the preceding estimate is adjusted to reflect the percent of use of the chemical on the commodity, the food factor is 20% of that normally expected for cottonseed (0.15 x 20% = .03%) and 2.5% of the citrus food factor (3.81% x 2.5% = .095%). The use adjusted estimated daily dietary exposure is 1.36×10^{-5} mg/kg/day.

3. Application exposures are less well defined. The August 9, 1982 memo from S. Creeger (EFB) to Mountfort provides some estimated risks to mixer/sprayers, pilots and flagmen under varying assumptions. It concludes that the data and therefore the estimates are unreliable. This report has been reviewed with R. Moraski of EFB who suggests that the Phase I exposure estimates shown in Table 1.2 (of the August 9, 1982 report) for pilots and flagmen are probably the most reliable available data. The exposure estimates have been calculated assuming 100% dermal absorption, as follows:

A. The worst case estimate has been calculated for

	Pilots	Flagmen
Avg. (ug/kg/hr)		
Forearm	3.8	959
Head	2.6	1628
Respiratory	0.48	13.8
	6.88	2600.8
Times 4 hrs/day	27.52 ug/kg/d	10,403.2 ug/kg/d
divided by 1000	.0275 mg/kg/d	10.4 mg/kg/d

B. The average daily life-time estimate has been pro rated by a 1/2 life time (35/70 years) x 1/10 of 365 days/yr use.

Pilot = .027 x .5 x .1 = 0.00135 mg/kg/d
Flagman = 10.4 x .05 = 0.52 mg/kg/d

Quantitative Estimates of Risk

The experimental data can be fitted to mathematical models which estimate the low-dose risk levels under various assumptions. Because the assumptions underlying these models cannot be experimentally verified it becomes important to demonstrate the reliability of the study data. The adjustment of study data by dietary and inter-species constants, which are also subject to undefined error, further confounds the reliability of the model and the dose-response relationship estimated. Given the limitations of the data noted above there seems to be little if any scientific justification for the quantitation of carcinogenicity risks associated with MAA based on the WARF Institute Chronic Feed Study in Rats.

Nevertheless, following the recommendation of Mantel-Bryan (JNCI Vol. 2, 1961), it might be prudent to evaluate the worst case evidence based on statistical tolerance considerations defined by confidence bounds on the dose-response relationship. Accordingly the data have been fitted to the log-probit and one-hit models to provide estimates of the lower 95% confidence bounds for doses (Virtually Safe Doses) associated with selected levels of attributable risk of cancer.

Defined Levels of Cancer Risk Implied by the Control & High Dose* Data from the WARF Chronic MAA Feeding Study in Rats

Mantel-Bryan Virtually Safe Dose Level Estimates (Lower 95% C.B.)	Attributable levels of Cancer Risk	One-Hit Model Virtually Safe Dose Levels	
		M L E	L. 95% C.B.
2.45×10^{-5}	1×10^{-8}	1.45×10^{-7}	7.23×10^{-8}
6.35×10^{-5}	1×10^{-7}	1.45×10^{-6}	7.23×10^{-7}
1.77×10^{-4}	1×10^{-6}	1.45×10^{-5}	7.23×10^{-6}
5.45×10^{-4}	1×10^{-5}	1.45×10^{-4}	7.23×10^{-5}
1.92×10^{-3}	1×10^{-4}	1.45×10^{-3}	7.23×10^{-4}
8.16×10^{-3}	1×10^{-3}	1.45×10^{-2}	7.23×10^{-3}
(mg/kg/d)	1×10^{-2}	1.46×10^{-1}	7.26×10^{-2}

The slope of the data may be calculated directly as 0.0613 or using the one-hit model the maximum likelihood estimate (MLE) of the slope is as 0.0689 and slope of the 95% confidence bound on the maximum likelihood estimator, Q_1^*, is 0.138. The risks associated with the six Environmental Exposures discussed above have been estimated directly using Crump's Global 79 program for the multi-stage model:

* As this is a feeding study in rats in which dose is estimated in ppm of diet, the data have been converted to mg/kg/d using Lehman's factor of 20 ppm = 1 mg/kg/d and from rat to man using a surface area correction of $\left(\frac{60{,}000 \text{ or } 70{,}000}{500}\right)^{1/3} \sim 5$; so that 200 ppm in the rat is equivalent to 2 mg/kg/d in man.

Type of Exposure	mg/kg/d Exposure	Upper 95% Bound on the Risk of Cancer	
		One-Hit Model	Mantel-Bryan
Dietary			
TMRC	3.6×10^{-4}	4.98×10^{-5}	$< 1 \times 10^{-6}$
Use Adjusted TMRC	1.36×10^{-5}	1.88×10^{-6}	$< 1 \times 10^{-8}$
Pilots			
Exposure Per Day	2.75×10^{-2}	3.80×10^{-3}	$> 1 \times 10^{-2}$
Life-time Pro-rated Daily	1.35×10^{-3}	1.87×10^{-4}	$\sim 1 \times 10^{-4}$
Flagmen			
Exposure Per Day	10.4	7.63×10^{-1}	$> 1 \times 10^{-2}$
Life-time Pro-rated Daily	5.2×10^{-1}	6.94×10^{-2}	$> 1 \times 10^{-2}$

Conclusions

The results of low-dose extrapolation of thyroid follicular tumor data in rats to risks of cancer in man suggest that we can be 95% certain that: 1) current tolerance levels granted to date (cottonseed and citrus) should present no more than a 5.0×10^{-5} (5/100,000) risk of cancer; 2) the risks of .07-.7 for flagmen and .0038 to .0002 for pilots clearly point up the need for protective clothing; 3) the primary problem with the data are that they possess almost equal potential for over-stating or understating the mathematically derived risks.

The bottom line seems to be that:

1. There is a risk to pilots and flagmen which should be addressed.

2. The apparent dietary risks are at the 5/100,000 but as the true risk may be either worse, or less, an additional study seems indicated.

Bertram Litt, Biostatistician
Toxicology Branch
Hazard Evaluation Division

Attachment

Attachment

Review:

1. SUBJECT: Summary - Thyroid Histopathology

TABLE: 1

	Males					Females				
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
Dose in Feed (ppm)	0	25	50	100	200	0	25	50	100	200
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	2/9	0/20	4/15	2/20	0/7	1/20	0/35	1/34	3/42	0/3
Autolysis - evaluated	24	29	32	32	21	9	17	20	14	28
Denominator	[42]	[26]	[28]	[33]	[47]	[41]	[28]	[21]	[17]	[44]
Not remarkable	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
hyperplastic, follicular										
diffuse	0	0	0	0	0	0	0	1	0	0
focal	0	0	0	0	2	0	0	0	0	1
hyperplastic, medullary cell										
focal	0	0	0	0	1	0	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

2. Statistical analysis of the above data using One Tail P Statistic of Fisher compared 4 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).

This statistical analysis gave a p = .021 which is statistically significant.

Follicular Ca + AdnCa	0	0	1	0	3	1	0	3	2	0
	2/42	0/26	3/28	1/33	8/47	2/46	2/23	3/21	2/19	4/44
Para Follicular Ca + AdnCa	0	0	0	0	1	0	0	1	0	0
	2/42	2/26	2/28	1/33	5/47	2/46	0/23	3/21	1/19	1/44