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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Atrazine Registration Standard + *Applic Exp*

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INTRODUCTION

Atrazine is a triazine herbicide that is used to selectively control annual broad-leaf and grass weeds in corn, sorghum and other crops. It is also used in forests and in Christmas tree plantations, turf, fence rows and rights-of-way.

In terms of pounds active ingredients applied annually, atrazine is one of the two most widely used agricultural pesticides in the United States.

ENVIRONMENTAL FATE

Atrazine is persistent in both water and soil. Atrazine and its degradates are also mobile. Therefore, atrazine poses a potential for contamination of both ground and surface water. Atrazine is among the most commonly occurring pesticides found in ground water. The percentage of detections greatly increases in high-use areas with vulnerable hydrogeologic environments.

A special data call-in (DCI) was sent to the registrant on November 2, 1988. The need for any additional retrospective ground water monitoring studies will be made after these data are received and analyzed.

1/7

Toxicology Branch Peer Review Committee classifying Atrazine as a C oncogen. Although the Peer Review Committee felt that quantitative risk assessment (using the Weibull model) was not appropriate considering the current data base, it was their opinion that the oncogenicity risk should be taken into consideration by using an additional uncertainty factor of 10 with the traditional RfD, which is usually an uncertainty factor of 100. It was also their intent that, when oncogenicity was concerned, that this uncertainty factor be increased by a factor of 10. In the case of Atrazine, this results in a MOE level of 1000, below which there is toxicologic concern for oncogenicity.

The NOEL used for the above calculations is 0.5 mg/kg/day obtained from the 1 year dog feeding study. The lesion of concern was cardiotoxicity.

SECTION I DETERMINATION OF CARDIOTOXICITY CONCERN

Risk for this toxic endpoint is evaluated by a MOS. This is derived by the following equation:

$$\text{MOS} = \text{NOEL}/\text{daily exposure (see table 4)}$$

The NOEL is based on the most sensitive toxicologic indicator (cardiac toxicity in the dog chronic feeding study, 0.5 mg/kg/day) and the exposure is the actual daily exposure to the applicator taking dermal absorption into account (Tables 1, 2 and 3). While it may be considered extreme to use an endpoint from a chronic study, it is deemed appropriate for the following reasons:

- 1) An acceptable subchronic dog study is not available.
- 2) The supplementary 90-day dog study that is available, does not have a NOEL established at the low dose (5 mg/kg/day) due to decreased bodyweight gain in males.
- 3) Although there were no histologic cardiac effects observed in this study, electrocardiography was not conducted. This parameter appeared to be the most sensitive indicator of cardiotoxicity in the dog.

Until such time as an appropriate subchronic study is conducted, the chronic NOEL for the dog will be used for determining the MOS for cardiotoxicity.

Table 4 presents the MOS for applicator exposures. These are for actual absorption plus potential absorption (due to material remaining on the skin after washing). MOSs of less than 100 are considered to be of toxicologic concern depending upon the number of days of exposure per year. For example, the MOS for Corn (grower open pour), Macedonia nuts (all) and Lawns

In order to reevaluate the appropriate risk characterization model, the Agency needs information on the following:

- 1) Hormone/receptor effects of Atrazine, including serum estrogen and other endocrine levels (including prolactin if possible);
- 2) Comparison of oncogenic potential between Fischer and Sprague-Dawley female rats; and is requiring an oncogenicity study for the Fischer rat;
- 3) Comparative metabolism between Fischer and Sprague-Dawley female rats, and between other mammalian species."

CARDIAC TOXICITY

Atrazine has been shown to produce cardiotoxicity in a one year feeding study in dogs. The NOEL is 0.5 mg/kg/day. This study is used to calculate the RfD for atrazine (as discussed in tolerance reassessment). The chronic study is being used to evaluate subchronic applicator risk, for the following reasons.

- 1) Cardiac effects (electrocardiographic) were reported in the chronic dog study at the low-effect-level at 175 days and at higher doses as early as 85 days.
- 2) An acceptable subchronic dog study is not available.
- 3) The supplementary 90-day dog study (00163339) that is available does not have a NOEL established at the low dose (5 mg/kg/day due to decreased bodyweight gain in males.
- 4) Although there were no histologic cardiac effects observed in the subchronic study, electrocardiography was not conducted. This parameter appears to be the most sensitive indicator of cardiotoxicity in the dog in the chronic study.

Until such time as an appropriate subchronic study is conducted, the chronic NOEL for the dog should be used for determining the MOS for cardiotoxicity.

TABLE 1 APPLICATOR EXPOSURE (not corrected for dermal absorption)

		(A) Annual exposure mg/kg/yr	(B) Day length of exposure hours	(C) Duration of exposure hours	(D) Exposure in days	(E) Exposure per day mg/kg/day	(F) Dose/day/ cm ² skin mg/cm ²	
Corn								
Grower open pour	M/L	5.2	4.5	8.9	2	2.60	0.06	
	A	1.2	4.5	8.9	2	0.60	0.01	
	M/L/A	6.4	4.5	8.9	2	3.20	0.07	
Commercial open	M/L	160.0	5.3	80.0	15	10.67	0.25	
	A	11.0	5.3	80.0	15	0.73	0.02	
	M/L/A	170.0	5.3	80.0	15	11.33	0.26	
Commercial closed	M/L	2.6	5.3	80.0	15	0.17	0.004	
	A	11.0	5.3	80.0	15	0.73	0.02	
	M/L/A	14.0	5.3	80.0	15	0.93	0.02	
Aerial closed	M/L	2.4	0.42	6.3	15	0.16	0.004	
	Pilot	0.1	0.42	6.3	15	0.007	0.0002	
Sugarcane								
Ground open	M/L	80.0	5.3	79.2	15	5.33	0.12	
	closed	M/L	1.3	5.3	79.2	15	0.09	0.002
	A	5.2	5.3	79.2	15	0.35	0.008	
Aerial closed	M/L	2.8	0.47	14.2	30	0.09	0.002	
	pilot	A	0.1	0.47	14.2	30	0.003	0.00007
	flagger		0.7	0.47	14.2	30	0.02	0.0005
Macedonia nuts								
Ground driver	M/L	3.2	11.7	35.0*	3	1.07	0.02	
	Single applicator	M/L/A	70.0	11.7	35.0*	3	23.33	0.54
	Split application	M/L/A	37.0	8.8	17.5*	2	18.50	0.43
Lawns								
Commercial	M/L	10.0	4.0	80.0*	20	0.50	0.01	
	A	220.0	4.0	80.0*	20	11.00	0.25	
Homeowner	M/L/A	0.2	1.0	1.2	2	0.10	0.002	

(A) - Actual annual exposure for each specific use pattern.
 (B) - Length of work day for each specific use pattern.
 (C) - Actual duration of exposure per year for each specific use pattern.
 (D) = (C)/(B) ; Calculated # of days of exposure per year for each specific use pattern.
 (E) = (A)/(D) ; Calculated exposure per work day for each specific use pattern.
 (F) = 70(E)/3000 ; actual daily dose assuming a 70 kg person and 3000 cm² skin exposed.
 * Incorrectly reported in memorandum of 7/18/88, Zendzian to Copley.

4

been received and evaluated. The adequacy of tolerances for atrazine in livestock will be reassessed following receipt of requested data on metabolism, analytical methods, and crop residues.

In addition, the Atrazine Guidance Document dated ~~9/85~~^{11/83} identified residue chemistry data gaps for animal metabolism, residue analytical methods and field residue studies. Data submitted in response to these requirements and all previously reviewed data have been evaluated to determine their adequacy for meeting current regulatory requirements.

The plant metabolism requirement is only partially complete, data depicting the total terminal residues of radiolabeled atrazine in corn is still required. The metabolism of atrazine in meat, poultry and eggs is not adequately understood, because major portions of the radiolabeled residues were not identified.

Residue analytical methods must be developed and validated which will quantify free and bound residues of the atrazine hydroxymetabolites. Plant and animal tissue samples bearing residues of atrazine chlorometabolites and hydroxymetabolites must be subjected to analysis by the multiresidues protocols.

The sample storage conditions and intervals must be supplied for all required and previously submitted residue data. Data are also required which depict the decline in levels of atrazine residues in commodities stored under the range of conditions and intervals specified.

Toxicology Endpoint: The routine chronic TAS analysis used a reference dose (ADI) of 0.005 mg/kg body weight/day, based upon a NOEL of 0.48 mg/kg body weight/day and a safety factor of 100 from a 1 year dog feeding study. The ADI has been approved by Division (06/03/88) and Agency (06/22/88) reference dose committees.

The Toxicology Peer Review Committee recently determined that atrazine is a Category C (possible human) oncogene for which quantitative risk assessment is inappropriate. The Committee also decided that the reference dose (RfD) used by the Office of Pesticide Programs did not adequately account for the oncogenic

ATRAZINE

APPLICATOR EXPOSURE

TABLE 3 APPLICATOR EXPOSURE
ADJUSTED FOR ACTUAL AND POTENTIAL DERMAL PENETRATION

		(J)	(K)	(L)	(M)
		Actual absorbed mg/kg/day	Total potential absorption mg/kg/day	Adjusted for lifetime exposure Actual absorbed mg/kg/day	Total potential absorption mg/kg/day
Corn					
Grower open pour	M/L	.009	0.49	.0000256	.00138
	A	.007	0.13	.0000204	.000358
	M/L/A	.01	0.61	.0000470	.00169
Commercial open	M/L	.04	2.03	.000789	.0424
	A	.009	0.16	.000187	.00328
	M/L/A	.04	2.15	.000838	.0450
Commercial closed	M/L	.002	0.04	.0000442	.000776
	A	.009	0.16	.000187	.00328
	M/L/A	.01	0.20	.000238	.00418
Aerial closed	M/L	.001	0.04	.0000224	.00130
	Pilot	.00005	0.002	.00000093	.0000331
Sugarcane					
Ground open closed	M/L	.02	1.01	.000395	.0212
	M/L	.001	0.02	.0000221	.000388
	A	.004	0.08	.0000883	.00155
Aerial closed pilot flagger	M/L	.0006	0.02	.0000261	.000929
	A	.00002	0.0007	.0000631	.0000331
		.0001	0.005	.00000652	.000232
Macedonia nuts					
Ground driver	M/L	.006	0.23	.000394	.000948
Single applicator	M/L/A	.06	2.52	.000249	.0103
Split application	M/L/A	.05	2.00	.000132	.00545
Lawns					
Commercial	M/L	.006	0.11	.000170	.00299
	A	.04	2.12	.00108	.0583
Homeowner	M/L/A	.0007	0.02	.00000186	.0000663

(J) = (E) (G) ; Actual absorbed compound on a workday.

(K) = (E) (I) ; Actual plus potential absorbed compound on a workday.

(L) = 35(A) (G)/[(70) (365) (L)] ; Daily lifetime exposure (based on actual absorption), assumes 35 working years, and 70 years lifespan, 365 days/year.

(M) = 35(A) (I)/[(70) (365) (L)] ; Daily lifetime exposure (based on actual plus potential absorption), assumes 35 working years, and 70 years lifespan, 365 days/year.

All Tier II data on Nontarget Area Phytotoxicity are required for herbicides used in forest and natural grasslands. Because of the wide variety of uses and fairly nonselective herbicidal activity, atrazine may have the potential to cause adverse effects on nontarget and endangered plant species.

Atrazine is presently being considered in formal consultation with the U.S. Fish and Wildlife Service (FWS) Office of Endangered Species for both crop and non-crop herbicide uses. Specific recommendations will be issued if USFWS determines endangered species are in jeopardy from these uses of atrazine.

Attachment