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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: ID:100-529; Atrazine; Assessment of risk to applicators due to oncogenicity and cardiotoxicity.

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WJ Brun 11/12/88

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Caswell file

CONCLUSIONS:

Risk to applicators is presented in terms of Margin of Safety (MOS) for cardiotoxicity concerns and range from < 1 to 714 when actual plus potential dermal exposure and penetration are considered. The majority of uses result in a MOS of less than 100 (see table 4). MOSs of less than 100 are considered to be of toxicologic concern depending upon the number of days of exposure per year (see section I).

Risk to applicators is presented in terms of Margin of Exposure (MOE) for oncogenicity concerns and ranges from 9 to 15106 when actual plus potential dermal exposure and penetration are considered. Many of the uses result in a MOE of less than 1000 (see table 4). MOEs of less than 1000 are considered to be of toxicologic concern (see section II).

BACKGROUND:

Atrazine is oncogenic (mammary tumors) in rats but not mice. A Registration Standard was completed in 1983 and a FRSTR is currently scheduled for early 1989. The Scientific Advisory Panel (SAP), in September, 1988 concurred with the

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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:

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

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

(homeowner) are all less than 25, however the applicators are only exposed for 2 or 3 days, depending upon use. Therefore the toxicologic concern is deminished for these uses. The concern remains for all other uses with MOS of less than 100.

SECTION II ONCOGENICITY CONCERN

The Peer Review Committee has determined that quantitation of risk using the Weibull model (Q_1^*) is inappropriate (draft Peer Review Reevaluation for Atrazine in response to the SAP). Therefore the risk will be presented as a MOE (Table 4). This is derived from the following equation:

$MOE = NOEL / \text{estimated lifetime exposure (in terms of mg/kg/day)}$

where the NOEL is as described above and the exposure is the applicator exposure adjusted for dermal absorption, lifetime (70 years), working years (35 years) (table 1 and 2).

As mentioned in the background, MOEs of less than 1000 are considered to be of toxicologic concern for oncogenicity. This is due to the Peer Review Committee's recommendation that, where oncogenicity was concerned, an additional factor of 10 be included with the uncertainty factor of 100, which is usually considered to be the cutoff for the level of concern.

Table 4 presents the MOE for applicator exposures. These are for actual absorption plus potential absorption (due to material remaining on the skin after washing).

TABLE 1 APPLICATOR EXPOSURE (not corrected for dermal absorption)

		(A) Annual exposure mg/kg/yr	(B) Day length hours	(C) Duration of exposure hours	(E) Exposure in days	(F) Exposure per day mg/kg/day	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	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.

ATRAZINE

APPLICATOR EXPOSURE

TABLE 2 RATES OF DERMAL ABSORPTION

		(G) Absorption rate (%)	(H) On washed skin (%)	(I) Total potential abs. exposure (%)
Corn				
Grower open pour	M/L	0.36	18.97	19.33
	A	1.24	20.56	21.80
	M/L/A	0.36	18.97	19.33
Commercial open	M/L	0.36	18.97	19.33
	A	1.24	20.56	21.80
	M/L/A	0.36	18.97	19.33
Commercial closed	M/L	1.24	20.56	21.80
	A	1.24	20.56	21.80
	M/L/A	1.24	20.56	21.80
Aerial closed	M/L	0.68	23.53	24.21
	Pilot	0.68	23.53	24.21
Sugarcane				
Ground open closed	M/L	0.36	18.97	19.33
	M/L	1.24	20.56	21.80
	A	1.24	20.56	21.80
Aerial closed pilot flagger	M/L	0.68	23.53	24.21
	A	0.68	23.53	24.21
		0.68	23.53	24.21
Macedonia nuts				
Ground driver	M/L	0.53	21.10	21.63
Single applicator	M/L/A	0.26	10.49	10.75
Split application	M/L/A	0.26	10.49	10.75
Lawns				
Commercial	M/L	1.24	20.56	21.80
	A	0.36	18.97	19.33
Homeowner	M/L/A	0.68	23.53	24.21

(G) & (H) - Taken from dermal absorption data evaluation report (7/18/88), adjusted for exposure duration and dose.

(I) = (G)+(H) ; Total potential rate of absorption accounting for both actual absorption and estimated potential absorption due to compound remaining of the skin after washing.

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
	M/L/A	.06	2.52	.000249	.0103
	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) = $\frac{E}{F}$ (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.

ATRAZINE

APPLICATOR EXPOSURE

TABLE 4 MARGIN OF SAFETY AND MARGIN OF EXPOSURE FOR APPLICATORS

		(N) <i>Conc'd</i>	(O) <i>over</i>
		Margin of Safety (MOS)	Margin of Exposure (MOE)
Corn			
Grower open pour	M/L	1**	362*
	A	4**	1397
	M/L/A	1**	296*
Commercial open	M/L	0.3*	12*
	A	3*	152*
	M/L/A	0.2*	11*
Commercial closed	M/L	13*	644*
	A	3*	152*
	M/L/A	3*	120*
Aerial closed	M/L	13*	385*
	Pilot	250	15105
Sugarcane			
Ground open	M/L	0.5*	24*
	closed	M/L	25*
	A	6*	323*
Aerial closed	M/L	25*	538*
	pilot	A	714
	flagger	100	2155
Macedonia nuts			
Ground driver	M/L	2**	527*
Single applicator	M/L/A	0.2**	49*
Split application	M/L/A	0.2**	92*
Lawns			
Commercial	M/L	5*	167*
	A	0.2*	9*
Homeowner	M/L/A	25**	7541

(N) = NOEL/(K) ; The NOEL is 0.5 mg/kg/day

(O) = NOEL/(M) ; The NOEL is 0.5 mg/kg/day

* - MARGINS OF TOXICOLOGIC CONCERN

** - MARGINS ARE LESS THAN 100 BUT EXPOSURE IS ONLY 1 OR 2 DAYS/YEAR