7-18-88

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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDOM

JUL 18 1988

SUBJECT: Atrazine, Recalculation of Oncogenic Risk Utilizing Data From a Rat Dermal Absorption Study

TO: Marion Copley DVM
Review Sec VI
Toxicology Branch

7/18/88

FROM: Robert P. Zendzian PhD
Senior Pharmacologist
Toxicology Branch
HED (TS-769)

Action requested

Attachment # I presents a number of oncogenic risk calculations from the use of atrizine. These risks are calculated on the basis of 100% dermal absorption. I have been requested to recalculate these risks based on the dermal absorption of atrazine determined experimentally in the following study;

Dermal absorption of ^{14}C-Atrazine by rats (general metabolism), T. Murphy, Biochemistry Dept., Agricultural Division, Ciba-Geigy Corp. Study No. ABR-87098; 11/6/87, MIRD 404313-08.

This document contains the following report which describes the in life portion of the study;

Dermal absorption of ^{14}C-Atrazine in Rats, E.M. Craine, WIL Research Laboratories, Project No. WIL-82015, 11/5/87.

A DER on this study is attached (II).

Discussion and conclusions.

Utilizing experimental data on dermal absorption in determining risk from field exposure is a two step process, first to determine the proper dermal absorption rate to be used for each exposure and second to apply that rate to the risk factor.

In the dermal absorption study the dose was applied as 0.01, 0.1 or 1.0 mg/cm^2 of skin and the absorption of each dose determined for exposure periods of 2, 4, 10 and 24 hours.

The exposure data are presented as mg/kg/yr. These must be converted to mg/cm^2/day and the daily duration determined for each exposure. The appropriate dermal absorption rate is then taken from the experimantally derived data. Table 1 presents the results of this process. The daily dermal dose per cm^2 of skin was calculated by multiplying the daily dose in mg/kg by 70 kg and dividing by 3000 cm^2. These are standard values for worker mass and for surface area exposed in a worker who does not wear protective clothing. In all cases except the home owner it is assumed that atrazine remains on the skin for 10 houre before the worker washes. The homeowner is assumed to wash after one hour of use. Two values to be used for risk calculations are determined, the absorption rate (% of dose) and the quantity remaining on the skin after soap and water wash (% of dose).

Table 2 presents the calculation of oncogenic risk. These values are calculated from oncogenic risk values determined by assuming 100% dermal absorption (attachment I) simply by multiplying them by the appropriate dermal absorption values. The first risk value utilizes only the percent absorbed. This value can be considered an overestimate of the risk since the rat skin is more permiable than that of man, a factor of five is usually accepted. The second value assumes the worst case, that the atrazine remaining on the skin after a soap and water wash is absorbable, and it includes both absorbed and retained material. We have no data as to whether and to what extent human skin would retain atrazine.

Including the the atrazine remaining on the washed skin as potentially absorbable adds considerably to the risk as from 12 to 40 times more atrazine remains on the skin after washing than was absorbed. If the risks calculated on the basis of absorbing all the material remaining on the skin are ultimately considered unacceptable, an additional dermal absorption study can be performed to determine the absorption of this material. Doses of 0.01, 01 and 1.0 mg/cm^2 should be applied to groups of 16 rats for 10 hours and then washed off with soap and-water. Total absorption should be determined on groups of 4 rats per dose for durations of 10 hours and 1, 7 and 14 days. The Registrant should submit a protocol for approval prior to performing the study.

Attachments.

Table 1. Determination of the dermal absorption rates to be used for each exposure scenario.

TABLE 1

		Annual Exposure mg/kg/yr	Duration of exposure hours	Exposure per day[a] mg/kg/day	Dose/day/ cm^2 skin[b] mg/cm^2	Absorption Rate (%) (/10 hrs)	On Washed Skin (%) (/10 hrs)
Corn							
Grower open pour	M/L	5.2	8.9	5.2	0.12	0.53	21.10
	A	1.2	8.9	1.2	0.03	2.00	24.87
	M/L/A	6.4	8.9	6.4	0.15	0.53	21.10
Commercial open	M/L	160.0	80	20	0.47	0.53	21.10
	A	11.0	80	1.4	0.03	2.0	24.87
	M/L/A	170.0	80	21.3	0.5	0.26	10.24
Commercial closed	M/L	2.6	80	0.3	0.007	2.00	24.87
	A	11.0	80	1.4	0.03	2.00	24.87
	M/L/A	14.0	80	1.8	0.04	2.00	24.87
Aerial closed	M/L	2.4	6.3	2.4	0.06	0.53	21.10
	Pilot	0.1	6.3	0.1	0.002	2.00	24.87
Sugercane							
ground open	M/L	80.0	79.2	1.0	0.02	2.00	24.87
closed	M/L	1.3	79.2	0.2	0.005	2.00	24.87
	A	5.2	79.2	0.7	0.02	2.00	24.87
Aerial closed	M/L	2.8	14.2	1.4	0.03	2.00	24.87
pilot	A	0.1	14.2	0.05	0.001	2.00	24.87
flagger		0.7	14.2	0.4	0.009	2.00	24.87
Macadonia nuts							
ground driver	M/L	3.2	8	3.2	0.07	0.53	21.10
single applicator	M/L/A	70.0	8	70.0	1.6	0.26	10.49
split application	M/L/A	37.0	8	37.0	0.86	0.26	10.49
single applicator	A	67.0	8	67.0	1.56	0.26	10.49
split application	A	34.0	8	34.0	0.79	0.26	10.49
Lawns							
Commercial	M/L	10.0	600	0.2	0.005	2.00	24.87
	A	220.0	600	3.7	0.09	0.53	21.10
Homeowner	M/L/A	0.2	1.2	0.2	0.005	0.11[c]	25.06[c]

a maximum of 10 hours per day
b assume 3000 cm^2 of skin exposed
c rate for one hour

Table 2. Determination of oncogenic risk using dermal absorption rates obtained from a study of the dermal absorption of atrazine in the rat. These values are calculated from oncogenic risk values determined by assuming 100% dermal absorption and multiplying them by the appropriate dermal absorption values. The first risk value utilizes only the percent absorbed. This value can be considered an overestimate of the risk since the rat skin is more permiable than that of man, a factor of five is usually accepted. The second value assumes the worst case, that the atrazine remaining on the skin after a soap and water wash is absorbable, and it includes both absorbed and retained material. We have no data as to whether and to what extent human skin would retain atrazine.

		Absorption Rate (%) (/10 hrs)	On Washed Skin (%) (/10 hrs)	Oncogenic risk % dose absorbed	Oncogenic risk % dose absorbed plus % on skin	
Corn						
Grower open pour	M/L	0.53	21.10	6×10^{-6}	2×10^{-4}	10^{-4}
	A	2.00	24.87	5×10^{-6}	7×10^{-5}	
	M/L/A	0.53	21.10	7×10^{-6}	3×10^{-4}	
Commercial open	M/L	0.53	21.10	2×10^{-5}	7×10^{-3}	10^{-2}
	A	2.00	24.87	5×10^{-5}	6×10^{-4}	
	M/L/A	0.26	10.24	9×10^{-5}	4×10^{-3}	
Commercial closed	M/L	2.00	24.87	1×10^{-5}	1×10^{-4}	
	A	2.00	24.87	5×10^{-5}	6×10^{-4}	
	M/L/A	2.00	24.87	6×10^{-5}	8×10^{-4}	10^{-3}
Aerial closed	M/L	0.53	21.10	3×10^{-6}	1×10^{-4}	
	Pilot	2.00	24.87	4×10^{-6}	6×10^{-6}	
Sugercane						
ground open	M/L	2.00	24.87	3×10^{-4}	5×10^{-3}	
closed	M/L	2.00	24.87	5×10^{-6}	7×10^{-5}	10^{-4}
	A	2.00	24.87	2×10^{-5}	3×10^{-4}	
Aerial closed	M/L	2.00	24.87	1×10^{-5}	2×10^{-4}	
pilot	A	2.00	24.87	4×10^{-7}	6×10^{-6}	
flagger		2.00	24.87	3×10^{-6}	4×10^{-5}	
Macadonia nuts						
ground driver	M/L	0.53	21.10	3×10^{-6}	1×10^{-5}	
single applicator	M/L/A	0.26	10.49	4×10^{-4}	2×10^{-3}	
split application	M/L/A	0.26	10.49	2×10^{-4}	8×10^{-4}	10^{-3}
single applicator	A	0.26	10.49	4×10^{-5}	2×10^{-3}	
split application	A	0.26	10.49	2×10^{-5}	8×10^{-4}	10^{-3}
Lawns						
Commercial	M/L	2.00	24.87	4×10^{-5}	6×10^{-4}	
	A	0.53	21.10	4×10^{-4}	1×10^{-2}	
Homeowner*	M/L/A	0.11*	25.06*	5×10^{-8}	1×10^{-5}	

* one hour exposure per day

Attachment # 7

Annual exposure at the representative use sites are listed below with the concomitant daily risk assessment.

		ESTIMATED ANNUAL EXPOSURE mg/kg/yr	ONCOGENIC RISK
CORN			
Grower open pour	M/L	5.2	1.1 x 10-3
8.9 lbs/yr	A	1.2	2.5 x 10-4
	M/L/A	6.4	1.3 x 10-3
Commercial open	M/L	160.0	3.3 x 10-2
50 lbs/yr	A	11.0	2.3 x 10-3
	M/L/A	170.0	3.5 x 10-2
Commercial closed	M/L	2.6	5.4 x 10-4
	A	11.0	2.3 x 10-3
50 lbs/yr	M/L/A	14.0	2.9 x 10-3
Aerial closed	M/L	2.4	5.0 x 10-4
1.3 lb/yr	Pilot A	0.1	2.1 x 10-5
SUGARCANE			
Ground open	M/L	80.0	1.7 x 10-2
closed	M/L	1.3	2.7 x 10-4
> 2.2 lbs/yr	A	5.2	1.1 x 10-3
Aerial closed	M/L	2.8	5.8 x 10-4
pilot	A	0.1	2.1 x 10-5
14.22 lbs flagger		0.7	1.5 x 10-4
MACADAMIA NUTS			
Ground driver	M/L	3.2	6.6 x 10-4
5 lbs Single applicator	M/L/A	70.0	1.5 x 10-2
Split application	M/L/A	37.0	7.7 x 10-3
Single applicator	A	67.0	1.4 x 10-2
Split application	A	34.0	7.1 x 10-3
LAWNS			
Commercial*	M/L	10.0	2.1 x 10-3
600 lbs	A	220.0	4.6 x 10-2
Homeowner*	M/L/A	0.2	4.1 x 10-5
1 lb 12 min			

* assumed no protective gloves

The above estimates have assumed 100% dermal absorption. The exposure for macadamia nuts and lawn turf uses are based on

Data Evaluation Report 006718

Compound Atrazine

Citation

Dermal absorption of ^{14}C-Atrazine by rats (general metabolism), T. Murphy, Biochemistry Dept., Agricultural Division, Ciba-Geigy Corp. Study No. ABR-87098; 11/6/87, MIRD 404313-08.

This document contains the following report which describes the in life portion of the study;

Dermal absorption of ^{14}C-Atrazine in Rats, E.M. Craine, WIL Research Laboratories, Project No. WIL-82015, 11/5/87.

Reviewed by Robert P. Zendzian Ph.D. 3/15/88
Senior Pharmacologist

Core Classification Acceptable

Conclusions

Atrazine in 4L formulation is absorbed in relatively small amounts through the skin. Typical values are 2.00, 0.53 and 0.26 % for 10 hour exposures to doses of 0.01, 0.1 or 1.0 mg/cm^2. Significant quantities remain on the skin after washing with soap and water (24.87, 21.10 and 10.49 %). No significant differences in absorption were observed between the 4L and 80W formulations tested at 1.0 mg/cm^2 for 10 hours. The data indicate that absorption is approaching saturation at the high dose.

Materials

Artazine uniformly ring labeled,

low and mid doses
22.0 uCi/mg, 99.5%

high doses
2.3 uCi/mg, 99.0%

Crl:CD®BR male rats 27-41 days old from Charles River Breeding laboratories

Experimental design and methods

Dose preparation and sample analysis was performed at Ciba-Geigy and the in life portion of the study at WIL.

"The low dose was prepared by mixing throughly 4.0 mg of ^{14}C-Atrazine and 5.3 mg of the formulant (4L), then suspending the mixture in 2.0 ml of deionized water. The middose was

prepared by mixing 40 mg of ^{14}C-Atrazine and 53.0 mg of blank formulation (4L) and then suspending the mixture in 2.0 ml of deionized water."

"The 4L high dose formulation was prepared by mixing throughly 530 mg of formulant and 400.0 mg of ^{14}C-Atrazine, then suspending the mixture in 4.0 ml of water. The 80W high dose was prepared by mixing 200.0 mg of ^{14}C-Atrazine and 50.0 mg blank formulant, then suspending the mixture in 2.0 ml of deionized water.

Two groups of 16 and one group of 20 male rats were treated dermally with single doses of ^{14}C-atrazine at 0.1, 1.0 and 10.0 mg/rat (0.01, 0.1 and 1.0 mg/cm^2) respectively. Four animals at each dose were dosed with 4L formulation and exposed for 2, 4, 10 and 24 hours. The remaining four animals at 10.0 mg/rat were dosed with 80W formulation and exposed for 10 hours.

"The test material preparations were stored frozen, warmed to room temperature and sonicated 10 minutes prior to analysis and dosing on the appropriate test material application day."

The anterior dorsal hair was shaved from each rat and the area washed with acetone 24 hours prior to dosing. Test material was applied to a 2.5 x 4 cm (10cm^2) area by pipette. The application site was covered with a protective device consisting of a stomahesive bandage as a wall and a filter paper cover.

Animals were individually caged in metabolism cages and total urine and feces collected.

Animals were sacrificed at the end of the exposure period. The protective device was removed and washed. The application site was washed with a detergent solution and water rinsed.

Blood, application site skin, skin under the bandage and the carcass were collected.

The following samples from each animal were sent to Ciba-Geigy for analysis;

"pipet washes, urine, feces, washes, extracts, samples from the protective coverings, gauze, blood, skin samples and carcasses,"

Results

Sample analysis for radioactivity at WIL indicated that dosing suspensions were homogenous and of the expected activity.

No compound-related effects on the rats were reported.

7

006718

Dermal absorption data is summarized in Table 1 below and presented in detail in Tables III - VI of the report.

Table 1. Summary of dermal absorption data. All values are means of 4 animals. All animals dosed with 4L formulation except as noted. Data from Tables III - VI of the report.

Dose (mg/cm^2)	Exposure (hours)	Absorbed[a] (%)	Absorbed[a] (%/hr)	Absorbed[a] ($mgx10^{-5}$)	On skin[b] (%)	Unabsorbed[c] (%)
0.01*	2	0.68	0.34	6	23.53	77.25
0.009†	4	1.24	0.31	11	20.56	71.88
	10	2.00	0.20	18	24.87	69.51
	24	4.93	0.21	44	20.72	69.02
0.1	2	0.21	0.11	20	25.06	71.55
0.095	4	0.36	0.09	34	18.97	75.72
	10	0.53	0.05	50	21.10	78.93
	24	1.26	0.05	119	29.04	67.43
1.0	2	0.13	0.06	107	11.24	88.67
0.82	4	0.09	0.02	74	14.69	88.00
	10	0.26	0.03	213	10.49	89.29
	24	0.21	0.01	172	9.58	91.03
1.0 80W 1.02	10	0.24	0.02	244	8.81	89.15

* Nominal dose.
† Applied dose.
a. Total of blood, carcass, urine and feces.
b. Total of skin I and skin II.
c. Total of bandage rinse, bridge rinse, paper rinse, soap rinse, water rinse, gauze A, gauze B and cage wash.

Discussion

The percent of dose absorbed followed the most common pattern of absorption with the percent increasing with time and decreasing with increasing dose. Significant quantities of test material remained on/in the skin following soap and water wash. There are clear indications that the process is approaching saturation at the high dose in that;

1. The percent absorbed per hour decreased with time in each dose and the proportionate decrease was larger with increasing dose.

2. As the dose increased the total quantities absorbed increased proportionately less per dose increase.

3. The quantity on/in the skin increased ten fold from 0.01 to 0.1 mg/cm^2 but only five fold from 0.1 to 1.0 mg/cm^2.

For regulatory purposes the test material which remains on/in the skin after soap and water wash is considered absorbable. For risk assesments the percent absorbed is added to the percent on/in the skin to determining quantity absorbed. However, the possibility exists that the relatively large quantity remaining on/in the skin is an artifact of the experimental procedure. A recent study, designed to determine if the material remaining on/in the skin after washing could be absorbed, showed that 2 to 3 times more material could be washed from the skin of living animals then from the skin of recently sacrificed animals. In this study the animals were sacrificied before washing the application site.

This possibility may be tested by treating 4 animals per dose for 10 hours exactly as was done in this study but washing the appliction site before sacrificing the animals. The ten hour exposure time is suggested as modeling a worker who washes at the end of the working day.

TR Review Dated 7/18/88

Page____ is not included in this copy.

Pages 10 through 13 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

✓ FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.