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

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM January 26, 1996

SUBJECT: Atrazine, Metabolism Studies

TO: Melba Morrow DVM
Review Sec II
Toxicology Branch I
Health Effects Division (7509C)

1/26/96

FROM: Robert P. Zendzian Ph.D.
Senior Pharmacologist
Toxicology Branch I
Health Effects Division (7509C)

DP Barcode # D215354, D215358, D215359 & D215361 Case #838836

Submission # S486944, S486954, S486958 & S486963

Chemical Atrazine ID #80803 Registrant CIBA-GEIGY

MRID # 435986-03, 04, 05 & 06

Action Requested

Evaluate the following reports and review those that are acceptable;

MRID 435986-04
Analysis of human urine to determine residues of atrazine, G-28273, G-28279 and G-30033 resulting from oral ingestion of atrazine including storage stability results. M.W. Cheung. Ciba-Geigy Greenboro NC. Laboratory Study Number ABR-90034. March 7, 1990

Human metabolism
Scientifically Acceptable Not a guideline study

Six adult male humans dosed with a single oral dose of 0.1 mg/kg. Total urine collected for 7 days and analyzed for atrazine and thiozine metabolites. Mean recovery; atrazine <0.01%, G-28273 (2,4-diamino-6-chloro-s-triazine) 7.70%, G-28279 (2-amino-4-choloro-6-ethylamino-striazene) 1.36% and

G-30033 (2-amino-4-choloro-6-isopropylamino-s-triazine) 5.30% of dose. Total thiozines 14.4% of dose.

MRID 435986-03
Metabolism and Kinetics of Atrazine in Man. Ivan W.F. Davidson, Department of Physiology/Pharmacology, Bowman Gray School of Medicine, WInston Salem, NC, Laboratory Project Number 101947. undated

The report contains a zerographic copy of the following document;

Metabolism and Kinetics of Atrazine in Man. Ivan W.F. Davidson, Department of Physiology/Pharmacology, Bowman Gray School of Medicine, WInston Salem, NC, Laboratory Project Number 101947.

This document is the report of a kinetic analysis of the data generated in study MRID 435986-04. The document analyzes blood and urinary excretion data from the study. The document is incomplete as it does not contain tables of the data analyzed, sufficent description of analytical methods utilized and references to support the conclusions re the metabolic pathways for atrazine that are discussed therein. The results cannot be verified independently and the report was not reviewed.

MRID 435986-05
Triazine urine monitoring. J.M. Baranyai. Ciba-Geigy. undated.

This report is an anlysis of urinary monitoring for astrazine metabolites conducted at the Ciba-Geigy St. Gabriel manufacturing plant in October 1989 and its application to atrizine risk assessment. It is not a report of the urinary monitoring project. The conclusions cannot be independently verified and the report was not reviewed.

MRID 435986-06
The in vitro percutaneous absorption of formulated [U-^{14}C]-Triazine G 30027 (Atrazine) and [U-^{14}C]-Triazine G 27692 (Simazine) through human and rat abdominal epidermis. L. Jack, Inveresk Research International Ltd. Laboratory Study Number IRI 154697.Dec 16, 1994.

Not a guideline study
The Study is scientifically unacceptable

The report is of an in vitro dermal absorption study. At this time no data have been presented which show that the in vitro methodology used in this study (the isolated epidermal membrane) accurately represents in vivo dermal absorption in the same species. An evaluation of all published data and data presented to the Agency on comparative in vivo and in vitro dermal penetration studies is in progress. None of the

in vitro methodologies available have been shown to reliably present in vivo dermal absorption. In vitro methodology has been show to err by either under or over estimating in vivo dermal absorption in an unpredictable manner. One methodology of a particular chemical in man overestimated at a low dose, matched at an intermediate dose and underestimated at a high dose. The report was not reviewed.

Conclusions

MRID 435986-04 reports an acceptable study of the urinary excretion of chlorothiozine metabolites following oral dosing of adult male humans. It provides data that may be used in the urinary monitoring of humans for atrazine exposure. However, it must be noted that MRID 435986-03 refers to blood samples taken during this study and there is no mention of blood sampling in this report.

MRID 435986-03, MRID 435986-05 and MRID 435986-06 are unacceptable and were not reviewed.

Attachment
DER
1-liner

Data Evaluation Report

Compound Atrazine

Study Type Metabolism human, not a guideline study

Citation

Analysis of human urine to determine residues of atrazine, G-28273, G-28279 and G-30033 resulting from oral ingestion of atrazine including storage stability results. M.W. Cheung. Ciba-Geigy Greenboro NC. Laboratory Study Number ABR-90034. March 7, 1990 MRID 435986-04

1/26/99

Reviewed by Robert P. Zendzian PhD
Senior Pharmacologist

Core Classification Acceptable

Conclusions

Six adult male humans dosed, single oral dose of 0.1 mg/kg. Total urine collected for 7 days. Urine analyzed for atrazine and thiozine metabolites. Mean recovery; atrazine <0.01%, G-28273 (2,4-diamino-6-chloro-s-triazine) 7.70%, G-28279 (2-amino-4-choloro-6-ethylamino-striazene) 1.36% and G-30033 (2-amino-4-choloro-6-isopropylamino-s-triazine) 5.30% of dose. Total 14.4% of dose.

Materials

Atrazine, CIBA-GEIGY code; G-30027
Purity 98.8%

Experimental design

Six adult human male volunteers received a single oral dose of 0.1 mg/kg Atrazine by capsule. Total urine was collected quantitatively for seven days prior to and seven days after dosing. Urine was analyzed for atrazine and its thiozine metabolites, G-28273 (2,4-diamino-6-chloro-s-triazine) G-28279 (2-amino-4-choloro-6-ethylamino-striazene) and G-30033 (2-amino-4-choloro-6-isopropylamino-s-triazine). Subjects maintained normal activity and dietary patterns during the test period.

Analytical standards for atrazine and the thiozine metabolites were provided by Production Technical Analytical Services Department, CIBA-GIEGY, Greensboro NC. Information on the test chemicals is provided in Table 1 from the report. Chemical structures are provided in Figure 1 from the report. Analytical procedures and standard responses are adaquately

described in the report. Sample stability tests were performed and it was determined that the standard chemicals were stable for a minimum of 11 days under ambient temperatures and a minimum of six months under refrigeration.

Results

No treatment related effect was observed on the pattern of urinary excretion during the test period. No physical signs or symptoms attributable to dosing were reported by the volunteers.

No atrazine or metabolites were detected in the pretreatment urine samples at the limit of detection. Atrazine was not detected in the postreatment urine at the limit of detection (0.005 ppm).

The chlorothiazine metabolites detected are reported as atrazine equivalents by correction for molecular weight.

Daily excretion of metabolites, in micrograms, is presented in Table IV from the report. In five of the volunteers the major urinary metabolite was G-28273 but in volunteer A02 the major metabolite was G-30033.

Daily excretion of metabolites, as percent of dose, is presented in Table VI from the report. Total cholortriazine accountability, as percent of dose is presented in Table VII from the report.

II. MASTER DATA TABLES AND OTHER GRAPHIC PRESENTATION

A. TABLES

TABLE I: TEST CHEMICALS

A. Atrazine: 2-chloro-4-ethylamino-6-isopropylamino-s-triazine,

Lot Number:	S85-0653-3
Expiration date:	2/88
Purity:	98.8%
Biochem. Inventory #	B04378

B. G-28273: 2,4-diamino-6-chloro-s-triazine

Lot Number:	S86-0939
Expiration date:	2/88
Purity:	97.0%
Biochem. Inventory #	B04379

C. G-28279: 2-amino-4-chloro-6-ethyl-amino-s-triazine

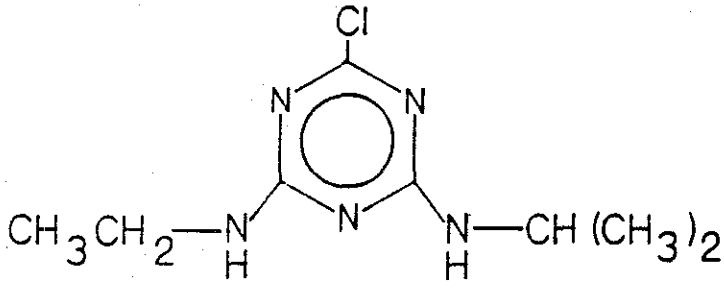
Lot Number:	S85-0727
Expiration date:	3/92
Purity:	98%
Biochem. Inventory #	B04516

D. G-30033: 2-amino-4-chloro-6-isopropylamino-s-triazine

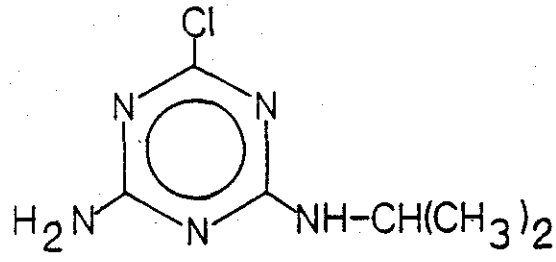
Lot Number:	S85-710
Expiration date:	7/91
Purity:	99%
Biochem. Inventory #	B04517

B. FIGURES

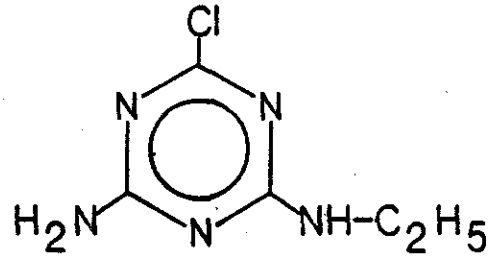
FIGURE 1. CHEMICAL NAMES AND STRUCTURES



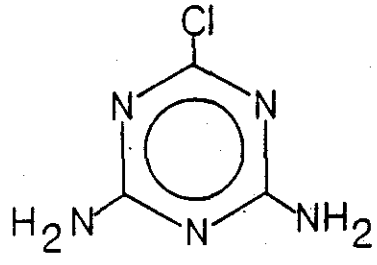
Atrazine
G-30027
2-Chloro-4-ethylamino-6-isopropylamino-s-triazine



G-30033
2-Amino-4-chloro-6-isopropylamino-s-triazine



G-28279
2-Amino-4-chloro-6-ethylamion-s-triazine



G-28273
2,4-Diamino-6-chloro-s-triazine

TABLE IV. AVERAGE DAILY CHLOROTRIAZINE EXCRETION (MICROGRAMS) BY TEST SUBJECTS

A. G-28273 (micrograms)

MALE	A01	A02	A03	A04	A05	A06		
AGA	10210	10211	10212	10213	10214	10215	AVERAGE	STD DEV
DAY								
0	352.80	396.20	517.64	701.20	355.40	501.70	470.82	133.45
1	125.20	111.22	161.78	150.93	88.07	220.29	142.92	46.33
2	55.21	32.01	38.08	38.90	32.15	57.38	42.29	11.25
3	14.02	4.87	3.99	7.39	0.00	7.76	6.34	4.59
4	0.00	0.00	0.00	0.00	0.00		0.00	
5	0.00	0.00	0.00	0.00			0.00	
6	0.00	0.00	0.00	0.00			0.00	
TOTAL	547.23	544.30	721.49	898.42	475.62	787.13	662.37	165.44

B. G-28279 (micrograms)

MALE	A01	A02	A03	A04	A05	A06		
AGA	10210	10211	10212	10213	10214	10215	AVERAGE	STD DEV
DAY								
0	45.49	59.99	59.67	78.46	77.28	142.07	77.16	34.11
1	6.63	5.42	71.68	53.16	2.88	86.92	37.78	37.51
2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
TOTAL	52.12	65.41	131.35	131.62	80.16	228.99	114.94	65.06

C. G-30033 (micrograms)

MALE	A01	A02	A03	A04	A05	A06		
AGA	10210	10211	10212	10213	10214	10215	AVERAGE	STD DEV
DAY								
0	364.43	717.27	386.24	484.42	200.73	526.18	446.55	174.28
1	10.23	11.85	12.70	0.00	0.00	2.63	6.23	6.00
2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
TOTAL	374.66	729.12	398.94	484.42	200.73	528.81	452.78	176.45

TABLE VI. DAILY CHLOROTRIAZINE ACCOUNTABILITY
(GROUP: A01-A06)

Percent Accountability

A. G-28273

MALE	A01	A02	A03	A04	A05	A06		
AGA	10210	10211	10212	10213	10214	10215	AVERAGE	STD DEV
DAY								
0	3.02	5.08	6.64	7.30	4.80	6.04	5.48	1.53
1	1.07	1.43	2.07	1.57	1.19	2.65	1.69	0.60
2	0.47	0.41	0.49	0.41	0.43	0.69	0.48	0.11
3	0.12	0.06	0.05	0.08	0.00	0.09	0.07	0.04
4	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
TOTAL	4.68	6.98	9.25	9.36	6.43	9.48	7.7	1.98

B. G-28279

MALE	A01	A02	A03	A04	A05	A06		
AGA	10210	10211	10212	10213	10214	10215	AVERAGE	STD DEV
DAY								
0	0.39	0.77	0.77	0.82	1.04	1.71	0.92	1.36
1	0.06	0.07	0.92	0.55	0.04	1.05	0.45	0.46
2	0.00	0.00	0.00	0.00	0.00	0.00		
TOTAL	0.45	0.84	1.68	1.37	1.08	2.76	1.36	0.81

C. G-30033

MALE	A01	A02	A03	A04	A05	A06		
AGA	10210	10211	10212	10213	10214	10215	AVERAGE	STD DEV
DAY								
0	3.11	9.20	4.95	5.05	2.71	6.34	5.23	2.36
1	0.09	0.15	0.16	0.00	0.00	0.03	0.07	0.07
2	0.00	0.00	0.00	0.00	0.00	0.00	0.00	
TOTAL	3.20	9.35	5.11	5.05	2.71	6.37	5.30	2.40

D. TOTAL CHLOROTRIAZINE

MALE	A01	A02	A03	A04	A05	A06		
AGA	10210	10211	10212	10213	10214	10215	AVERAGE	STD DEV
DAY								
0	6.52	15.04	12.35	13.17	8.56	14.10	11.62	3.35
1	1.22	1.65	3.16	2.13	1.23	3.73	2.19	1.05
2	0.47	0.41	0.49	0.41	0.43	0.69	0.48	0.11
3	0.12	0.06	0.05	0.08	0.00	0.09	0.07	0.04
TOTAL	8.33	17.16	16.05	15.79	10.22	18.61	14.36	4.55

TABLE VII. TOTAL CHLOROTRIAZINE ACCOUNTABILITY

	PERCENT OF DOSE[1]				
	ATRAZINE	G-30033	G-28279	G-28273	TOTAL
A01	<0.10	3.20	0.45	4.68	8.32
A02	<0.10	9.35	0.84	6.98	17.2
A03	<0.10	5.11	1.68	9.25	16.1
A04	<0.10	5.05	1.37	9.36	15.8
A05	<0.10	2.71	1.08	6.43	10.2
A06	<0.10	6.37	2.76	9.48	18.6
	<0.10	5.30 ± 2.40	1.36 ± 0.81	7.70 ± 1.98	14.4 ± 4.11

[1]G-28273, G-28279 and G-30033 expressed as atrazine equivalents

Tox Chem No. Atrazine File Last Updated _____ Current Date _____

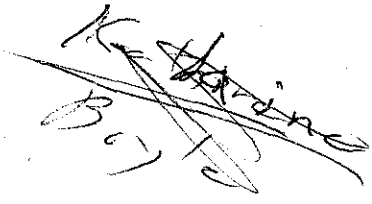
Study/Lab/Study #/Date	Material	EPA MRID No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
Metabolism, Human; CIBA-GEIGY; ABR-90034; Mar 7, 1990	atrazine	435986-04	Six adult male humans dosed, single oral dose of 0.1 mg/kg. Total urine collected for 7 days. Urine analyzed for atrazine and thiozine metabolites. Mean recovery; atrazine <0.01%, G-28273 (2,4-diamino-6-chloro-s-triazine) 7.70%, G-28279 (2-amino-4--choloro-6-ethylamino-striazene) 1.36% and G-30033 (2-amino-4-choloro -6-isopropylamino-s-triazine) 5.30% of dose. Total 14.4% of dose.	N/A	Acceptable

Dermal absorption studies of atrazine in my files 1/24/96
I have reviews of some of these and a risk assesment comparing blood concentrations by oral and dermal routes

Atrazine
Dermal absorption of ^{14}C-Atrazine by rats (general metabolism), G.J. Marco, Biochemistry Dept., Agricultural Division, Ciba-Geigy Corp. Study No. ABR-83005; 5/16/83, MIRD 404313-11. (151796)

Atrazine
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.

Atrazine
A dermal radiotracer absorption study in rats with ^{14}C-Atrazine. C.P. Chengelis. WIL Research Laboratories. WIL Study no 82048. June 22, 1994. MRID 433143-02.



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

7/15/88

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	% dose absorbed plus % on skin
Corn					
Grower open pour	M/L	0.53	21.10	6×10^{-6}	2×10^{-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}
	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}
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}
	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}
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}
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 lb/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 lb/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 lb/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 lb/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
14.2 lb/ flagger		0.7	1.5 x 10-4
MACADAMIA NUTS			
Ground driver	M/L	3.2	6.6 x 10-4
5 lb 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 lb	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.

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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.

TABLE III: THE PERCENT OF DOSE ABSORBED[1], UNABSORBED[2], AND REMAINING ON THE SKIN AFTER A SOAP AND WATER RINSE IN ANIMALS TREATED WITH ^{14}C-ATRAZINE AT THE LOW DOSE LEVEL[3]

Fraction	Low Dose (0.1 mg/Rat) Time of Sacrifice (Hours)			
	2	4	10	24
Blood	0.11	0.08	0.10	0.14
Carcass	0.51	1.04	1.37	1.93
Urine	0.06	0.12	0.53	2.53
Feces	0.00	0.00	0.00	0.33
	0.68	1.24	2.00	4.93
Skin I	20.53	18.14	22.33	18.38
Skin II	3.00	2.42	2.54	2.34
Σ Skin	23.53	20.56	24.87	20.72
Absorbed[1]	24.21	21.80	26.87	25.65
Bandage Rinse	0.04	0.07	0.08	0.21
Bridge Rinse	0.16	0.01	0.03	0.03
Paper Rinse	0.07	0.27	0.23	0.55
Soap Rinse	69.46	63.99	61.40	59.74
Water Rinse	5.34	5.78	5.69	6.05
Paper	0.01	0.01	0.02	0.01
Gauze A	1.96	1.61	1.80	1.79
Gauze B	0.07	0.07	0.09	0.10
Cage Wash	0.14	0.07	0.17	0.54
Unabsorbed[2]	77.25	71.88	69.51	69.02
Total ^{14}C Recovered	101.46	93.68	96.38	94.67

[1]Sum of the blood, carcass, urine, feces, skin I, and skin II.

[2]Sum of the bandage rinse, bridge rinse, paper rinse, soap rinse, water rinse, paper, gauze A, gauze B, and cage wash.

[3]Mean of four animals per time point.

TABLE IV: THE PERCENT OF DOSE ABSORBED[1], UNABSORBED[2], AND REMAINING ON THE SKIN AFTER A SOAP AND WATER RINSE IN ANIMALS TREATED WITH ^{14}C-ATRAZINE AT THE MIDDOSE LEVEL[3]

Fraction	Mid Dose (1.0 mg/Rat) Time of Sacrifice (Hours)			
	2	4	10	24
Blood	0.01	0.01	0.01	0.03
Carcass	0.18	0.29	0.38	0.60
Urine	0.02	0.06	0.14	0.58
Feces	0.00	0.00	0.00	0.05
	0.21	0.36	0.53	1.26
Skin I	20.71	15.27	15.39	26.75
Skin II	4.35	3.70	5.71	2.29
Σ Skin	25.06	18.97	21.10	29.04
Absorbed[1]	25.27	19.33	21.63	30.30
Bandage Rinse	0.38	1.05	0.05	1.21
Bridge Rinse	0.01	0.25	0.01	0.01
Paper Rinse	0.02	0.02	0.05	0.10
Soap Rinse	61.53	66.66	70.96	57.28
Water Rinse	6.87	5.27	5.23	7.37
Paper	0.00	0.00	0.00	0.01
Gauze A	2.59	2.36	2.50	1.27
Gauze B	0.14	0.10	0.10	0.09
Cage Wash	0.01	0.01	0.03	0.09
Unabsorbed[2]	71.55	75.72	78.93	67.43
Total ^{14}C Recovered	96.82	95.05	100.56	97.73

[1]Sum of the blood, carcass, urine, feces, skin I, and skin II.

[2]Sum of the bandage rinse, bridge rinse, paper rinse, soap rinse, water rinse, paper, gauze A, gauze B, and cage wash.

[3]Mean of four animals per time point.

TABLE V: THE PERCENT OF DOSE ABSORBED[1], UNABSORBED[2], AND REMAINING ON THE SKIN AFTER A SOAP AND WATER RINSE IN ANIMALS TREATED WITH ^{14}C-ATRAZINE AT THE HIGH DOSE LEVEL[3]

Fraction	High Dose (10.0 mg/Rat) Time of Sacrifice (Hours)			
	2	4	10	24
Blood	0.01	0.00	0.00	0.00
Carcass	0.12	0.08	0.24	0.13
Urine	0.00	0.01	0.02	0.07
Feces	0.00	0.00	0.00	0.01
	0.13	0.09	0.26	0.21
Skin I	7.09	8.80	6.94	6.58
Skin II	4.15	5.89	3.55	3.00
Σ Skin	11.24	14.69	10.49	9.58
Absorbed[1]	11.37	14.78	10.75	9.79
Bandage Rinse	5.60	4.14	5.75	5.23
Bridge Rinse	0.02	0.02	0.05	0.00
Paper Rinse	0.01	0.01	0.02	0.02
Soap Rinse	76.42	76.98	77.92	77.36
Water Rinse	4.19	3.97	3.11	5.16
Paper	0.00	0.00	0.00	0.00
Gauze A	2.34	2.80	2.35	3.16
Gauze B	0.08	0.07	0.04	0.08
Cage Wash	0.01	0.01	0.05	0.02
Unabsorbed[2]	88.67	88.00	89.29	91.03
Total ^{14}C Recovered	100.04	102.78	100.04	100.82

[1]Sum of the blood, carcass, urine, feces, skin I, and skin II.

[2]Sum of the bandage rinse, bridge rinse, paper rinse, soap rinse, water rinse, paper, gauze A, gauze B, and cage wash.

[3]Mean of four animals per time point.

TABLE VI: COMPARATIVE DATA OF TWO DIFFERENT FORMULATIONS (4L VERSUS 80W) WITH ^{14}C-ATRAZINE TEN HOURS AFTER THE HIGH DOSE LEVEL[1,2,3]

Fraction	High Dose (10.0 mg/Rat) Formulation	
	4L	80W
Blood	0.00	0.00
Carcass	0.24	0.22
Urine	0.02	0.02
Feces	0.00	0.00
	0.26	0.24
Skin I	6.94	4.61
Skin II	3.55	4.20
Σ Skin	10.49	8.81
Absorbed[1]	10.75	9.05
Bandage Rinse	5.75	0.51
Bridge Rinse	0.05	0.02
Paper Rinse	0.02	0.01
Soap Rinse	77.92	81.22
Water Rinse	3.11	4.25
Paper	0.00	0.00
Gauze A	2.35	3.03
Gauze B	0.04	0.06
Cage Wash	0.05	0.05
Unabsorbed[2]	89.29	89.15
Total ^{14}C Recovered	100.04	98.20

[1]Sum of the blood, carcass, urine, feces, skin I, and skin II.

[2]Sum of the bandage rinse, bridge rinse, paper rinse, soap rinse, water rinse, paper, gauze A, gauze B, and cage wash.

[3]Mean of four animals per time point.

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

006718

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Mar 24,1988

MEMORANDOM

SUBJECT: Atrazine, Review of Dermal Absorption Studies

TO: Judith Hauswirth Ph.D
Section Head
Review Secion VI

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

Compound; Atrazine — Tox Chem #63

Registration #100-529 — Registrant; Ciba-Geigy

Accession #404313-08&-11 — Tox Project #8-0320A

Action Requested

Review the following studies

Dermal absorption of ^{14}C-Atrazine by rats (general metabolism), G.J. Marco, Biochemistry Dept., Agricultural Division, Ciba-Geigy Corp. Study No. ABR-83005; 5/16/83, MIRD 404313-11.

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.

Conclusions

Study No. MIRD 404313-11

Core Classification Unacceptable

In general the report was so poorly written as to make it impossible to determine the experimental design while the

methodology lacked sufficient detail to allow evaluation. However, deficiencies were identified that are sufficient to invalidate the study. These include the following;

1. Compound was applied in ethanol, not in the field solvent. Since the dermal absorption of a compound is dependent upon the solvent, use of the wrong solvent will produce unusable data.

2. The application site was not covered allowing material to flake off. This would both decrease the amount of material available for absorption and contaminate the urine and feces.

Study No. MRID 404313-08

Core Classification Acceptable

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.

Attachments

DERs
One-Liner

Data Evaluation Report 006718

Compound Atrazine

Citation

Dermal absorption of ^{14}C-Atrazine by rats (general metabolism), G.J. Marco, Biochemistry Dept., Agricultural Division, Ciba-Geigy Corp. Study No. ABR-83005; 5/16/83, MIRD 404313-11.

3/24/88

Reviewed by Robert P. Zendzian Ph.D.
Senior Pharmacologist

Core Classification Unacceptable

Conclusions

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Data Evaluation Report 006718

Compound Atrazine

Citation

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

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Reviewed by Robert P. Zendzian Ph.D. 3/5/88
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.

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] (%)	(%/hr)	($mgx10^{-5}$)	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.

TABLE III: THE PERCENT OF DOSE ABSORBED[1], UNABSORBED[2], AND REMAINING ON THE SKIN AFTER A SOAP AND WATER RINSE IN ANIMALS TREATED WITH ^{14}C-ATRAZINE AT THE LOW DOSE LEVEL[3]

Fraction	Low Dose (0.1 mg/Rat) Time of Sacrifice (Hours)			
	2	4	10	24
Blood	0.11	0.08	0.10	0.14
Carcass	0.51	1.04	1.37	1.93
Urine	0.06	0.12	0.53	2.53
Feces	0.00	0.00	0.00	0.33
	0.68	1.24	2.00	4.93
Skin I	20.53	18.14	22.33	18.38
Skin II	3.00	2.42	2.54	2.34
Σ Skin	23.53	20.56	24.87	20.72
Absorbed[1]	24.21	21.80	26.87	25.65
Bandage Rinse	0.04	0.07	0.08	0.21
Bridge Rinse	0.16	0.01	0.03	0.03
Paper Rinse	0.07	0.27	0.23	0.55
Soap Rinse	69.46	63.99	61.40	59.74
Water Rinse	5.34	5.78	5.69	6.05
Paper	0.01	0.01	0.02	0.01
Gauze A	1.96	1.61	1.80	1.79
Gauze B	0.07	0.07	0.09	0.10
Cage Wash	0.14	0.07	0.17	0.54
Unabsorbed[2]	77.25	71.88	69.51	69.02
Total ^{14}C Recovered	101.46	93.68	96.38	94.67

[1]Sum of the blood, carcass, urine, feces, skin I, and skin II.

[2]Sum of the bandage rinse, bridge rinse, paper rinse, soap rinse, water rinse, paper, gauze A, gauze B, and cage wash.

[3]Mean of four animals per time point.

TABLE IV: THE PERCENT OF DOSE ABSORBED[1], UNABSORBED[2], AND REMAINING ON THE SKIN AFTER A SOAP AND WATER RINSE IN ANIMALS TREATED WITH ^{14}C-ATRAZINE AT THE MIDDOSE LEVEL[3]

Fraction	Mid Dose (1.0 mg/Rat) Time of Sacrifice (Hours)			
	2	4	10	24
Blood	0.01	0.01	0.01	0.03
Carcass	0.18	0.29	0.38	0.60
Urine	0.02	0.06	0.14	0.58
Feces	0.00	0.00	0.00	0.05
	0.21	0.36	0.53	1.26
Skin I	20.71	15.27	15.39	26.75
Skin II	4.35	3.70	5.71	2.29
Σ Skin	25.06	18.97	21.10	29.04
Absorbed[1]	25.27	19.33	21.63	30.30
Bandage Rinse	0.38	1.05	0.05	1.21
Bridge Rinse	0.01	0.25	0.01	0.01
Paper Rinse	0.02	0.02	0.05	0.10
Soap Rinse	61.53	66.66	70.96	57.28
Water Rinse	6.87	5.27	5.23	7.37
Paper	0.00	0.00	0.00	0.01
Gauze A	2.59	2.36	2.50	1.27
Gauze B	0.14	0.10	0.10	0.09
Cage Wash	0.01	0.01	0.03	0.09
Unabsorbed[2]	71.55	75.72	78.93	67.43
Total ^{14}C Recovered	96.82	95.05	100.56	97.73

[1]Sum of the blood, carcass, urine, feces, skin I, and skin II.

[2]Sum of the bandage rinse, bridge rinse, paper rinse, soap rinse, water rinse, paper, gauze A, gauze B, and cage wash.

[3]Mean of four animals per time point.

TABLE V: THE PERCENT OF DOSE ABSORBED[1], UNABSORBED[2], AND REMAINING ON THE SKIN AFTER A SOAP AND WATER RINSE IN ANIMALS TREATED WITH ^{14}C-ATRAZINE AT THE HIGH DOSE LEVEL[3]

Fraction	High Dose (10.0 mg/Rat) Time of Sacrifice (Hours)			
	2	4	10	24
Blood	0.01	0.00	0.00	0.00
Carcass	0.12	0.08	0.24	0.13
Urine	0.00	0.01	0.02	0.07
Feces	0.00	0.00	0.00	0.01
	0.13	0.09	0.26	0.21
Skin I	7.09	8.80	6.94	6.58
Skin II	4.15	5.89	3.55	3.00
Σ Skin	11.24	14.69	10.49	9.58
Absorbed[1]	11.37	14.78	10.75	9.79
Bandage Rinse	5.60	4.14	5.75	5.23
Bridge Rinse	0.02	0.02	0.05	0.00
Paper Rinse	0.01	0.01	0.02	0.02
Soap Rinse	76.42	76.98	77.92	77.36
Water Rinse	4.19	3.97	3.11	5.16
Paper	0.00	0.00	0.00	0.00
Gauze A	2.34	2.80	2.35	3.16
Gauze B	0.08	0.07	0.04	0.08
Cage Wash	0.01	0.01	0.05	0.02
Unabsorbed[2]	88.67	88.00	89.29	91.03
Total ^{14}C Recovered	100.04	102.78	100.04	100.82

[1]Sum of the blood, carcass, urine, feces, skin I, and skin II.

[2]Sum of the bandage rinse, bridge rinse, paper rinse, soap rinse, water rinse, paper, gauze A, gauze B, and cage wash.

[3]Mean of four animals per time point.

TABLE VI: COMPARATIVE DATA OF TWO DIFFERENT FORMULATIONS (4L VERSUS 80W) WITH ^{14}C-ATRAZINE TEN HOURS AFTER THE HIGH DOSE LEVEL[1,2,3]

Fraction	High Dose (10.0 mg/Rat) Formulation	
	4L	80W
Blood	0.00	0.00
Carcass	0.24	0.22
Urine	0.02	0.02
Feces	0.00	0.00
	0.26	0.24
Skin I	6.94	4.61
Skin II	3.55	4.20
Σ Skin	10.49	8.81
Absorbed[1]	10.75	9.05
Bandage Rinse	5.75	0.51
Bridge Rinse	0.05	0.02
Paper Rinse	0.02	0.01
Soap Rinse	77.92	81.22
Water Rinse	3.11	4.25
Paper	0.00	0.00
Gauze A	2.35	3.03
Gauze B	0.04	0.06
Cage Wash	0.05	0.05
Unabsorbed[2]	89.29	89.15
Total ^{14}C Recovered	100.04	98.20

[1]Sum of the blood, carcass, urine, feces, skin I, and skin II.

[2]Sum of the bandage rinse, bridge rinse, paper rinse, soap rinse, water rinse, paper, gauze A, gauze B, and cage wash.

[3]Mean of four animals per time point.

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

JAN 11 1995

011388

[redacted]

MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SUBJECT: Atrazine, Dermal Absorption in Rats

TO: Walter Waldrop PM 71
Reregistration Branch
Special Review and Reregistration Division (7508C)

1/6/95

FROM: Robert P. Zendzian Ph.D.
Senior Pharmacologist
Toxicology Branch I
Health Effects Division (7509C)

THROUGH: Karl Baetcke Ph.D.
Chief
Toxicology Branch I
Health Effects Division (7509C)

1/6/95

Compound; Amatraz Tox Chem #063 PC CODE [redacted]#; 080803

Registrant; Ciba-Geigy MRID 433143-02 DP Barcode; D206233

Action Requested

Review the following study;

Study Type Dermal Absorption (85-3)

Citation
A dermal radiotracer absorption study in rats with ^{14}CAtrazine. C.P. Chengelis. WIL Reseaech Laboratories. WIL Study no 82048. June 22, 1994. MRID 433143-02.

Core Classification Acceptable

Conclusions
4 Male rats per dose and duration dosed at 0.01, 0.1 or 1 mg/cm^2. 0.5, 1, 2, 4, 10 and 24 hours exposure and 10 hours exposure, washed, to 34, 58 and 82 hours and 24 hours exposure, washed, to 48, 72 and 96 hours. Percent absorbed increased with time decreased with dose. Significant portion of dose remaining on washed skin with subsiquent absorbption. See DER for detailed data.

Effects of this new data, if any, on the atrazine risk assessent will be considered separately.

Attachment DER

Data Evaluation Report

Compound Atrazine

Study Type Dermal Absorption (85-3)

Citation

A dermal radiotracer absorption study in rats with ^{14}C-Atrazine. C.P. Chengelis. WIL Reseaech Laboratories. WIL Study no 82048. June 22, 1994. MRID 433143-02.

11/2/94

Reviewed by Robert P. Zendzian PhD
Senior Pharmacologist

Core Classification Acceptable

Conclusions

4 Male rats per dose and duration dosed at 0.01, 0.1 or 1 mg/cm^2. 0.5, 1, 2, 4, 10 and 24 hours exposure and 10 hours exposure, washed, to 34, 58 and 82 hours and 24 hours exposure, washed, to 48, 72 and 96 hours. Percent absorbed increased with time decreased with dose. Significant portion of dose remaining on washed skin with subsequent absorbption. See DER for detailed data.

Materials

Atrazine. ^{14}C
vial 1, CL-XXII-45
specific activity 1.9 uCi/mg
radio purity 98.7%
vial 2 & 3, CL-XXII-47
specific activity 19.1 uCi/mg
radio purity 98.9%
from Geigy

4L blank No FL 901240
Reference 82047-3

Male Charles River CD rats 30-32 days of age
from Charles River Portage Michigan

Experimental Design

Four rats per dose and exposure duration were dosed at 0.1, 1 or 10 mg/rat according to the dosing schedule given below. The application site was washed at 10 or 24 hours on the animals designated as exposed for 10 or 24 hours and subsiquently terminated at 34 to 96 hours

011388

Exposure Duration (hours)	Termination (hours)
0.5	0.5
1	1
2	2
4	4
10	10
24	24
10	34
10	58
10	82
24	48
24	72
24	96

Dose preportration

"For the low dose formulation 10.4 mg of blank 4L formulant was added to Vial No 2 (containing ^{14}C-Atrazine) followed by the addition of 4.0 ml of deionized water." The materal was mixed, sonicated and maintained on a magnetic stirring plate.

"For the mid dose formulation 104 mg of blank 4L formulant was added to Vial No 3 (containing ^{14}C-Atrazine) followed by the addition of 4.0 ml of deionized water." The materal was mixed, sonicated and maintained on a magnetic stirring plate.

"For the high dose formulation 1.04 gm of blank 4L formulant was added to Vial No 1 (containing ^{14}C-Atrazine) followed by the addition of 8.0 ml of deionized water." The materal was mixed, sonicated and maintained on a magnetic stirring plate.

All dosing suspensions were analyzed on the day of preparation and on each day of dosing before administration. Radiochemical purity was determined for each dosing suspension.

Application of test material

The back of each rat was shaved 24 hour prior to dosing and the shaved area washed with acetone. "Before application of the test material, a small linked stainless steel jewelers chain waas attached to shackle the rear legs of each rat to prevent scratching of the treated area. The skin of the dose area was defined and enclosed with a nonocclusive covering or "protective appliance", which consisted of a piece of Stomato-ahesive, filter paper and an aluminum bridge. The Stomahesive was affixed to the skin with Skin-Bond® cement to form a "well" surrounding the area of skin to be treated.

The treated area was covered with filter paper elevated by a foil bridge to prevent contact with the applied dose. The application site, within the "well", was a 10.0 cm^2 area (2.5 cm X 4.0 cm)."

Test material was applied with a positive displacement pipette and spread with the tip. The pipette was washed with ethanol to determine residual material. Actual dose applied was determined by subtraction. The rat was placed in a Nalgene metabolism unit and urine and feces collected separately for the entire exposure period.

At the end of the exposure period, the filter paper and foil bridge was removed and the application site washed with Liquid Dove in water and rinsed with water. Animals scheduled for termination at 0.5 to 24 hours were euthanized with CO^2. The abdominal cavity was opened and a 5 to 7 ml sample of blood taken from the inferior vena cava. The Stomatohesive was removed and the application site skin and the skin under the Stomatohesive were collected separately. Residual bladder urine was collected and added to the last urine collection. The residual carcass was collected.

Animals schedured to be terminated beyond 24 hours were returned to the origional metabolism unit. At termination these rats were again washed and terminated as above.

Samples analyzed were as follows:

Application device wash
Skin wash
Application site skin
Blood
Urine
Feces
Carcass

Results

Blood concentrations are presented in Table 3 and dose distribution in Tables 4, 5 and 6 from the report.

WIL-82048
CIBA-GEIGY CORPORATION
CIBA-GEIGY PROTOCOL NUMBER: 89-90-B

TABLE 3

The Average Concentrations of ^{14}C-Atrazine Equivalents in the Whole Blood of Each Sub-Group of Rats at Euthanization

Values were calculated from the data for individual rats presented in Appendix D.

Sub-Group Number	Time of Exposure (hours)	Time of Sacrifice (hours)	Group I (µg/g)	Group II (µg/g)	Group III (µg/g)
1	0.5	0.5	0.002	0.004	<0.019
2	1.0	1.0	0.003	0.004	0.019
3	2.0	2.0	0.004	0.006	0.023
4	4.0	4.0	0.003	0.007	<0.019
5	10.0	10.0	0.007	0.009	0.024
6	24.0	24.0	0.020	0.350 (0.224)*	0.026
7	10.0	34.0	0.030	0.128	0.251
8	10.0	58.0	0.044	0.165	0.688
9	10.0	82.0	0.045	0.280	1.351
10	24.0	48.0	0.037	0.254	0.249
11	24.0	72.0	0.046	0.569 (0.349)**	1.618 (1.183)*
12	24.0	96.0	0.054 (0.043)*	0.496 (0.401)*	1.701 (1.218)*

* Value in ( ) is that obtained if one animal is excluded because of apparent oral ingestion

**Value in ( ) is that obtained if two animals are excluded because of apparent oral ingestion

TABLE 4

The Average Disposition of Doses of ^{14}C-Atrazine Following a Single Dermal Exposure at a a Level of 9.13 $\mu g/cm^2$ (Group I)

Each value, expressed as a percent of the actual dose, represents the mean of four animals of a sub-group. Animals of a sub-group were exposed for the same time and were euthanized at the same time point after the start of exposure. Values were transferred from Appendices E, F, G, H, I, and J.

Duration of Exposure (hours)	Time Euthanized (hours)	Application Device Washes (%)	Skin Washes (%)	Associated with Skin at Site (%)	Blood (%)	Urine (%)	Feces (%)	Carcass (%)	Average Recovery of Applied 14C-Atrazine (%)	Average 14C-Atrazine Absorbed Direct Procedure (%)	Average 14C-Atrazine Absorbed Indirect Procedure (%)
0.5	0.5	2.22	73.41	24.20	0.01	0.00	0.00	0.19	100.02	0.20	0.18
1.0	1.0	1.32	71.11	28.04	0.01	0.02	0.00	0.52	101.02	0.55	-0.47
2.0	2.0	2.05	71.30	26.71	0.02	0.07	0.00	0.81	100.97	0.90	-0.06
4.0	4.0	2.49	69.90	27.55	0.02	0.20	0.00	0.71	100.86	0.93	0.07
10.0	10.0	1.24	67.13	28.63	0.04	0.64	0.02	1.18	98.88	1.88	3.01
24.0	24.0	1.21	55.66	30.77	0.15	3.82	0.46	3.46	95.51	7.88	12.37
10.0	34.0	1.45	73.60	6.75	0.17	7.41	1.97	3.76	95.10	13.30	18.20
10.0	58.0	1.54	67.42	4.87	0.25	13.20	4.04	3.67	94.98	21.15	26.17
10.0	82.0	1.20	64.84	5.11	0.34	13.88	4.38	3.00	92.76	21.60	28.84
24.0	48.0	2.18	65.10	7.22	0.19	10.71	2.40	4.73	92.54	18.04	25.50
24.0	72.0	1.95	59.70	4.35	0.28	14.73	5.16	3.79	89.95	23.95	34.00
24.0 *	96.0	3.28	51.46	4.21	0.36	19.08	8.13	3.58	90.10	31.15	41.05
		(1.81)	(61.06)	(4.90)	(0.25)	(15.51)	(5.72)	(2.93)	(92.18)	(24.40)	(32.22)

*Value in ( ) is that obtained if one animal is excluded because of apparent oral ingestion.

TABLE 5

The Average Disposition of Doses of ^{14}C-Atrazine Following a Single Dermal Exposure at a Level of 94.3 $\mu g/cm^2$ (Group II)

Each value, expressed as a percent of the actual dose, represents the mean of four animals of a sub-group. Animals of a sub-group were exposed for the same time and were euthanized at the same time point after the start of exposure. Values were transferred from Appendices E, F, G, H, I, and J.

Duration of Exposure (hours)	Time Euthanized (hours)	Application Device Washes (%)	Skin Washes (%)	Associated with Skin at Site (%)	Blood (%)	Urine (%)	Feces (%)	Carcass (%)	Average Recovery of Applied 14C-Atrazine (%)	Average 14C-Atrazine Absorbed: Direct Procedure (%)	Average 14C-Atrazine Absorbed: Indirect Procedure (%)
0.5	0.5	1.14	73.85	27.14	0.00	0.00	0.00	0.16	102.29	0.16	-2.13
1.0	1.0	1.05	82.81	21.20	0.00	0.00	0.00	0.12	105.17	0.12	-5.05
2.0	2.0	0.64	83.21	18.16	0.00	0.00	0.00	0.13	102.14	0.13	-2.01
4.0	4.0	1.70	78.90	20.54	0.00	0.03	0.00	0.18	101.34	0.21	-1.14
10.0	10.0	2.25	76.22	24.54	0.00	0.08	0.00	0.25	103.35	0.34	-3.01
24.0 *	24.0	3.54	45.58	30.88	0.19	7.22	1.33	6.29	95.03	15.03	20.01
		(3.16)	(54.32)	(31.60)	(0.11)	(4.12)	(0.63)	(4.24)	(98.19)	(9.11)	(10.92)
10.0	34.0	1.44	82.57	9.13	0.08	2.88	0.73	1.70	98.54	5.40	6.85
10.0	58.0	1.46	80.41	3.50	0.10	4.45	1.15	1.78	92.84	7.48	14.64
10.0	82.0	1.58	73.94	3.44	0.17	8.28	2.04	2.83	92.28	13.32	21.04
24.0	48.0	2.90	74.01	7.48	0.14	5.70	1.39	3.29	94.90	10.51	15.61
24.0 **	72.0	2.33	58.72	2.76	0.37	17.13	5.09	4.69	91.10	27.29	36.19
		(1.64)	(73.13)	(2.73)	(0.23)	(9.79)	(2.60)	(3.78)	(93.88)	(16.39)	(22.51)
24.0 *	96.0	1.36	61.98	2.45	0.30	17.63	6.80	3.67	94.17	28.40	34.22
		(1.29)	(65.20)	(2.73)	(0.26)	(15.99)	(6.53)	(3.46)	(95.46)	(26.24)	(30.78)

*Value in ( ) is that obtained if one animal is excluded because of apparent oral ingestion.
**Value in ( ) is that obtained if two animals are excluded because of apparent oral ingestion.

TABLE 6

The Average Disposition of Doses of ^{14}C-Atrazine Following a Single Dermal Exposure at a Level of 936 µg/cm^2 (Group III)

Each value, expressed as a percent of the actual dose, represents the mean of four animals of a sub-group. Animals of a sub-group were exposed for the same time and were euthanized at the same time point after the start of exposure. Values were transferred from Appendices E, F, G, H, I, and J.

Duration of Exposure (hours)	Time Euthanized (hours)	Application Device Washes (%)	Skin Washes (%)	Associated with Skin at Site (%)	Blood (%)	Urine (%)	Feces (%)	Carcass (%)	Average Recovery of Applied 14C-Atrazine (%)	Average 14C-Atrazine Absorbed: Direct Procedure (%)	Average 14C-Atrazine Absorbed: Indirect Procedure (%)
0.5	0.5	2.03	90.72	11.44	0.00	0.00	0.00	0.08	104.26	0.08	-4.18
1.0	1.0	3.89	91.50	9.05	0.00	0.00	0.00	0.08	104.51	0.08	-4.44
2.0	2.0	12.71	82.46	8.59	0.00	0.00	0.00	0.06	103.82	0.06	-3.76
4.0	4.0	3.40	90.00	9.85	0.00	0.01	0.00	0.07	103.32	0.07	-3.25
10.0	10.0	3.62	93.51	9.60	0.00	0.00	0.00	0.08	106.80	0.08	-6.72
24.0	24.0	9.39	80.61	14.16	0.00	0.06	0.01	0.07	104.29	0.14	-4.15
10.0	34.0	2.65	95.16	4.00	0.02	0.52	0.13	0.28	102.76	0.95	-1.81
10.0	58.0	2.13	92.02	3.03	0.05	2.14	0.51	0.71	100.58	3.41	2.83
10.0	82.0	2.19	87.66	2.25	0.09	4.26	1.30	0.87	98.62	6.52	7.90
24.0	48.0	3.41	90.92	8.34	0.02	0.63	0.12	0.39	103.83	1.16	-2.67
24.0 *	72.0	1.98	87.11	2.95	0.09	4.62	1.80	1.30	99.85	7.81	7.96
		(1.59)	(89.87)	(3.56)	(0.07)	(3.04)	(1.33)	(1.22)	(100.69)	(5.66)	(4.98)
24.0 *	96.0	2.26	88.91	2.14	0.10	5.41	1.54	0.91	101.27	7.96	6.69
		(1.92)	(90.82)	(2.60)	(0.08)	(3.77)	(1.12)	(0.84)	(101.14)	(5.81)	(4.66)

*Value in ( ) is that obtained if one animal is excluded because of apparent oral ingestion.

13544

056519

Chemical:	**Atrazine**
PC Code:	**080803**
HED File Code	**13000 Tox Reviews**
Memo Date:	**01/26/96**
File ID:	**DPD215354; DPD215358; DPD215359; DPD215361**
Accession Number:	**412-03-0019**

***HED* Records Reference Center**
12/31/2002