State of California

HSM-97001

Memorandum

[HSM no assigned after original issuance of memo]

To: Phil Anderson, Registration Specialist
Pesticide Registration Branch

Date: February 13, 1997

Place: Sacramento

445-4267

From: Department of Pesticide Regulation - Tom Thongsinthusak, Staff Toxicologist
Worker Health and Safety Branch
[original signed by T. Thongsinthusak]

Subject: PRODUCT NAME: Atrazine
ACTIVE INGREDIENT: Atrazine
COMPANY NAME: Ciba-Geigy Corporation
I.D. NUMBER: 160109-E
DOCUMENT NUMBER: 220-432
EPA REGISTRATION NUMBER: ----
TITLE: *In Vivo* Percutaneous Absorption of Atrazine in Man (Interim Report)

Surge Laboratory of the University of California, San Francisco conducted an *in vivo* dermal absorption studies of atrazine in human volunteers. The study was completed on October 25, 1995. As indicated in the submitted reports, this study was not conducted in compliance with the U.S. EPA Good Laboratory Practice Standards (40 CFR, part 160). However, the study director provided a written statement to indicate that this study was conducted under Good Scientific Practices and in general compliance with the spirit of Good Laboratory Practice Standards. The following provides a brief description and results of the study.

A. Human volunteers

Twelve healthy male volunteers, aged from 43 to 74 years, were recruited from the University of California, San Francisco, and the surrounding San Francisco Bay Area community. Six volunteers were used for group A (low dose) and six volunteers were used for group B (high dose). But, two volunteers were dismissed from the low dose group due to improper collection of urine samples on the first day.

B. Dose preparation and application

Volunteers in group A received a dose level of 6.7 $\mu g/cm^2$ (low dose) and those in group B received 79 $\mu g/cm^2$. The dosing solution was prepared by mixing the appropriate amount of [^{14}C]-atrazine (98.4 % pure) and 4L blank formulation in deionized water. The prepared dosing solution was applied to 25 cm^2 (2.0 cm x 12.5 cm) of the left ventral forearm of each volunteer. The application was accomplished by using a 0.1 mL Teflon coated syringe. After topical application, the dosed area was allowed to air dry. Then, a non occlusive plastic cover was secured over the dosed area and kept in place for 24 hours. The cover was shaped as a half round cylinder with three open holes on the top. This allowed air circulation from both sides and through the open holes on the top. The volunteers were instructed not to touch or wash the treated area for 24 hours.

C. Sample collection and analysis

At 24 hours after dosing, the plastic cover was removed and the treated skin was washed alternately with the Ivory liquid soap solution (50%, v/v) and deionized water for two cycles. The fifth washing was done with deionized water. At 168 hours after dosing, the dosed skin was stripped with cellophane tape 10 times. The volunteers were instructed to collect urine and feces samples one hour before dosing and according to the schedules shown in Tables A.1 and B.1. The samples were kept in a cooler containing dry ice and ice packs during each collection period. Samples collected for analysis were urine, feces, skin washes, tape strips, and non occlusive covers. All samples were prepared and radioactivity measurements were conducted by using a model 1500 Packard Liquid Scintillation Counter.

D. Results and discussion

Recoveries of the administered doses in urine and feces samples are shown in Tables A.1 and B.1. The (arithmetic) mean dose recovered in urine was 5.03% for the low dose and 1.11% for the high dose. Excretion of the dose in feces was much lower than that in urine. The majority of the administered dose was found in the skin wash sample (Tables A.2 and B.2) with a mean of 95.4% for the low dose and 91.0% for the high dose. The mass balance for both doses are very good: 101.2% for the low dose and 92.3% for the high dose.

As indicated in the same submitted report, an IV administration of atrazine was conducted in rhesus monkeys (Study No. UCSF95SU04), Ciba-Geigy #333-95). At 168 hours after a single IV dose, 84.84 ± 5.60% of the administered dose was recovered in urine and 11.73% ± 1.90% was recovered in feces; the overall recovery of the dose was 98.92 ± 5.87%. The studies in monkeys and in human volunteers revealed that atrazine is not likely to accumulate in tissues or blood after 168 hours following topical or IV administration. Based on these observations, the dermal absorption rate for atrazine is simply the total dose excreted in urine and feces. The estimated dermal absorption values were 5.6 ± 3.1% (Table A.3) for the low dose and 1.2 ± 1.0 % for the high dose (Table B.3).

E. Recommendations

The dermal absorption study of atrazine in human volunteers is appropriate for use in the determination of the dermal absorption rate. The low dose of 6.7 $\mu g/cm^2$ is more representative of exposure that agricultural workers would experience. The dermal absorption of 5.6% will be used in the determination of absorbed dosages of atrazine in humans. The dermal absorption of 1.2% for the high dose (79 $\mu g/cm^2$) may be appropriate for use in the determination of absorbed dosages of atrazine in formulation workers or to other workers who may experience a high level of exposure similar to the dose used in the dermal absorption study. These recommendations are based upon the assumption that data in the interim report will be the same as those in the final report.

cc: Jim Sanborn
John Ross

(TDW/Dermal/Atrazin1)

A. Dermal absorption of atrazine in human volunteers (Doc. No. 220-432; low dose - 6.7 ug/cm2).

Table A.1 Cumulative dose recovered in urine (U) and feces (F) samples.

	Interval (hrs)	% Dose Volunteer # A-01	Volunteer # A-02	Volunteer # A-03	Volunteer # A-06
Urine	0-4	0.0023	0.0019	0.0133	0.0004
	4-8	0.0199	0.1123	0.2391	0.0155
	8-12	0.0400	0.1819	0.7825	1.0119
	12-24	0.2625	0.9085	0.5998	0.3380
	24-48	1.1708	1.9438	3.7808	2.0665
	48-72	0.4356	0.6166	2.0161	0.4672
	72-96	0.0736	0.3775	0.8722	0.4035
	96-120	0.0222	0.1541	0.4003	0.2454
	120-144	0.0033	0.0630	0.1886	0.1209
	144-168	0.0000	0.0558	0.0472	0.0532
	Total	2.0302	4.4154	8.9399	4.7225
	Mean	5.03			
	SD	2.87			

	Interval (hrs)	% Dose Volunteer # A-01	Volunteer # A-02	Volunteer # A-03	Volunteer # A-06
Feces	0-24	0.0596	0.0000	0.0010	0.0165
	24-48	0.0641	0.1017	0.0244	0.3614
	48-72	0.0865	0.0427	0.2835	0.2562
	72-96	0.0105	0.0542	0.2281	0.1257
	96-120	0.0795	0.0141	0.1219	0.1030
	120-144	0.0000	0.0669	0.0260	0.0238
	144-168	0.0633	0.0414	0.0744	0.0952
	Total	0.3635	0.3210	0.7593	0.9818
	Mean	0.61			
	SD	0.32			

Table A.2 Mass balance.

	% Dose Volunteer # A-01	Volunteer # A-02	Volunteer # A-03	Volunteer # A-06	Mean	SD
Urine	2.0302	4.4154	8.9399	4.7225	5.03	2.87
Feces	0.3635	0.3210	0.7593	0.9818	0.61	0.32
Skin wash	96.456	93.6106	91.2667	100.1539	95.37	3.83
Tape strip	0.0016	0.0061	0.0025	0.0054	0.00	0.00
Cover	0.1183	0.2357	0.1505	0.0943	0.15	0.06
Total	98.9696	98.5888	101.1189	105.9579	101.2	3.4

Table A.3 Calculation of % dermal absorption.

	% Dose Volunteer # A-01	Volunteer # A-02	Volunteer # A-03	Volunteer # A-06
Urine	2.0302	4.4154	8.9399	4.7225
Feces	0.3635	0.3210	0.7593	0.9818
U+F	2.3937	4.7364	9.6992	5.7043
Mean (U+F)	5.63			
SD	3.05			

B. Dermal absorption of atrazine in human volunteers (Doc. No. 220-432; high dose - 79 ug/cm2).

Table B.1 Cumulative dose recovered in urine and feces samples.

		% Dose					
	Interval (hrs)	Volunteer # B-01	Volunteer # B-02	Volunteer # B-03	Volunteer # B-04	Volunteer # B-05	Volunteer # B-06
Urine	0-4	0.1365	0.0015	0.0364	0.0060	0.0117	0.0196
	4-8	0.2889	0.0190	0.0000	0.0147	0.0211	0.0458
	8-12	0.2766	0.0120	0.2173	0.0155	0.0000	0.0493
	12-24	0.7723	0.0257	0.2049	0.0784	0.1148	0.1311
	24-48	0.5572	0.1167	0.3869	0.2082	0.2181	0.2332
	48-72	0.4485	0.0664	0.1789	0.1049	0.1717	0.1904
	72-96	0.2050	0.0037	0.0605	0.0582	0.0771	0.1728
	96-120	0.0917	0.0069	0.0401	0.0348	0.0760	0.1293
	120-144	0.0638	0.0000	0.0120	0.0131	0.0242	0.0444
	144-168	0.0266	0.0000	0.0080	0.0095	0.0460	0.0688
	Total	2.8671	0.2519	1.145	0.5433	0.7607	1.0847
	Mean	1.11					
	SD	0.92					

		% Dose					
	Interval (hrs)	Volunteer # B-01	Volunteer # B-02	Volunteer # B-03	Volunteer # B-04	Volunteer # B-05	Volunteer # B-06
Feces	0-24	0.0345	0.0000	0.0182	0.0000	0.0000	0.0200
	24-48	0.1043	0.0000	0.0025	0.0000	0.0000	0.0067
	48-72	0.0690	0.0000	0.0139	0.0000	0.0000	0.0000
	72-96	0.0437	0.0000	0.0174	0.0004	0.0000	0.0682
	96-120	0.0061	0.0045	0.0000	0.0000	0.0002	0.0000
	120-144	0.0180	0.0000	0.0000	0.0005	0.0000	0.0000
	144-168	0.0000	0.0000	0.0000	0.0023	0.0000	0.0000
	Total	0.2756	0.0045	0.0520	0.0032	0.0002	0.0949
	Mean	0.07					
	SD	0.11					

Table B.2 Mass balance.

	% Dose							
	Volunteer # B-01	Volunteer # B-02	Volunteer # B-03	Volunteer # B-04	Volunteer # B-05	Volunteer # B-06	Mean	SD
Urine	2.8671	0.2519	1.145	0.5433	0.7607	1.0847	1.11	0.92
Feces	0.2756	0.0045	0.052	0.0032	0.0002	0.0949	0.07	0.11
Skin wash	90.2874	91.4773	89.9201	92.0318	87.0834	95.2985	91.02	2.71
Tape strip	0.0003	0.0010	0.0008	0.0007	0.0005	0.0003	0.0006	0.0003
Cover	0.1109	0.0078	0.0354	0.1566	0.0137	0.0377	0.06	0.06
Total	93.5413	91.7425	91.1533	92.7356	87.8585	96.5161	92.3	2.9

Table B.3 Calculation of % dermal absorption.

	% Dose					
	Volunteer # B-01	Volunteer # B-02	Volunteer # B-03	Volunteer # B-04	Volunteer # B-05	Volunteer # B-06
Urine	2.8671	0.2519	1.145	0.5433	0.7607	1.0847
Feces	0.2756	0.0045	0.052	0.0032	0.0002	0.0949
U+F	3.1427	0.2564	1.197	0.5465	0.7609	1.1796
Mean (U+F)	1.18					
SD	1.03					