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

DEC 31 1996

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OFFICE OF
PREVENTION, PESTICIDES, AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Atrazine, Review of Rhesus Monkey Metabolism and Human Dermal Absorption Studies

TO: Jackie McQueen PM 63
Special Review Branch
Special Review and Reregistration Division (7508C)

FROM: Robert P. Zendzian Ph.D. 10/25/96
Senior Pharmacologist
Science Analysis Branch
Health Effects Division (7509C)

THROUGH: William Burnam
Chief
Science Analysis Branch
Health Effects Division (7509C)

DP Barcode #D224158 Case #838836 Submission #S501484

Chemical #Atrazine ID #080803

Registrant #Ciba-Geigy MRID 439344-07,08,09&10

Action Requested

Review the following studies;

Citation

Disposition of atrazine in rhesus monkey following intravenous administration. Intrim Report. X. Hui, R.C. Wester and H.I. Maibach. UCSF 95SU04. June 19, 1995 MRID 439344-07

Core Classification Acceptable

Summary

Four adult female rhesus monkeys dosed IV with 0.260 mg ^{14}C-atrazine. Timed plasma, urine and fecal samples collected for analysis of ^{14}C-label. Plasma two compartment; t 1/2 a 1.5 hrs, t 1/2 b 17.7 hrs, C_{max} 0.0385 ug Atrazine/gm plasma, volume of distribution 1360 ml. 84.8 % of label excreted in urine at 168 hours, byphasic. 11.73 % of label excreted in feces at 168 hours.

Citation
Intrim Report. Disposition of atrazine in rhesus monkey following intravenous administration. H.I. Maibach. Ciba-Geigy. ABR-95131. Jan 29, 1995 MRID 439344-08

Core Classification Cannot be reviewed

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The data presented are from an early stage of the analysis and are grossly incomplete. No conclusions can be drawn from the data presented. The report was not reviewed.

Citation
In vivo percutaneous absorption of atrazine in man. Intrim report. X. Hui, R.C. Wester and H.I. Maibach. UCSF. Lab study No H832-11835-01. Oct 25, 1995. MRID 439344-09

Core Classification Acceptable

Summary
4 adult male humans dosed dermally at 6.7 ug/cm^2 for 24 hours, washed and followed to 168 hours. 5.64% absorbed. 6 adult male humans dosed dermally at 79 ug/cm^2 for 24 hours, washed and followed to 168 hours. 1.18% absorbed.

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Attachments
DERs

Data Evaluation Report

012127

Chemical Atrazine

Study Metabolism.. Intravenous kinetics

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Robert P. Zendzian Ph.D.
Senior Pharmacologist

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Materials

Atrazine U-ring-^{14}C-atrazine
white powder
chemical purity 96.5%
radiochemical purity 98.1%
specific activity 50.8 uCi/mg
from Ciba-Geigy

Propylene glycol
lot number ECL5088
colorless liquid
Wako Pure Chemical Industries Ltd.

Sterile 0.9% sodium chloride solution
lot number 5SH4612
Sigma Chemical Co.

Experimental Design

Four female Rhesus monkeys were dose intravenously with 0.26 + 0.01 mg ^{14}C-atrazine (13.35 + 0.37 uCi). Blood samples (4.0 ml) were collected at 0, 0.5, 1, 2, 4, 8 and 24 hours after dosing. Urine was collected for 24 hours prior to dosing; 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 hours after dosing. Fecal samples were collected for 24 hours prior to dosing; 0-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 hours after dosing.

Dose preparation

"Five mg of [^{14}C]-atrazine was dissolved in 130 ml of sterile 0.9% sodium chloride/ propylene glycol (2:1) for a final concentration of 0.00385% (w/v)." By analysis "One ml of the dosing solution contained 1.9673 $\pm$ 0.0037 uCi [^{14}C]-atrazine."

Dosing

"On the day of dosing, each animal was sedated with an intramuscular injection of 10 mg ketamine and 0.25 mg of xylocane per kg of body weight. A 20 guage Angiocath I.V. Cather (Derset Medical, Inc) was placed in the forearm cephalic vein for intravenous administration. A 20 guage Landmark Midline Cather (Menlo Care Inc.) was placed in the lower saphenous vein for blood sampling. A one ml syringe[1] containing the dosing solution was connected with the Angiocath I.V. catheter. An aliquot of the dosing solution (6.78 $\pm$ 0.19 ml) containing 0.26 $\pm$ 0.01 mg atrazine (13.35 $\pm$ 0.37 uCi) was administered to each monkey. Following the i.v. injection of the dosing solution, the catheter was flushed with 3 ml saline to clear the catheter of the [^{14}C]-atrazine and then it was removed. The delivered dose was quantitated by weight difference of the dosing syringe before and after dosing."

Samples analysed

Blood samples were separated into plasma and packed red cells and analysed separately. Urine samples were analysed directly and fecal samples were homogenized in water for analysis. Duplicates of all samples were analysed.

Results

Summary analytical results are attached in tables from the report as follows;

1. Table 2b, Summary of [^{14}C]-atrazine concentration of plasma as ug equivalents per gram.

2. Table 4b, Summary of [^{14}C]-atrazine concentration of packed blood cells as ug equivalents per gram.

3. Table 6c, Summary of urine concentration of [^{14}C]-atrazine as cumulative percent of dose.

4. Table 8c, Summary of fecal concentration of [^{14}C]-atrazine as cumulative percent of dose.

1. Typographial error should by a 10 ml syringe. Personal comm.

Discussion

Kinetics of the plasma concentration of radiolabel (as ^{14}C-atrazine) were analysed by a computer model. Results are presented in Table 11 from the report. Results of the analysis were verified by plotting the data (Figure A). Results are compared as follows;

	Model	Graph
Distribution phase half life (hrs)	1.50	1.9
Excretion phase half life (hrs)	17.71	17.5
Maximum plasma concentration (ug Eq/ml)	0.0385	0.0380
Volume of distribution (ml)	1361	1918

The differences are reasonable considering the individual animal variation.

Urinary excretion of label (as ^{14}C-atrazine) appears to be indicative of a biphasic pattern with a relative increase in excretion for the 72-96 and 96-120 hours collection periods. This is more clearly shown in Figure B. This is most likely due to the delayed excrteion of a metabolite of atrazine as the urinary excretion of label is the summation of the urinary excretion of metabolites.

Completion of the metabolite analysis (MRID 439344-08) is necessary to verify this conclusion.

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Page _____ is not included in this copy.

Pages 6 through 12 are not included in this copy.

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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.

Data Evaluation Report

Chemical Atrazine

Citation

Intrim Report. Disposition of atrazine in rhesus monkey following intravenous administration. H.I. Maibach. Ciba-Geigy. ABR-95131. Jan 29, 1995 MRID 439344-08

Reviewed by

10/25/95

Robert P. Zendzian Ph.D.
Senior Pharmacologist

Core Classification Cannot be reviewed

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Citation
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Reviewed by

10/24/96

Robert P. Zendzian Ph.D.
Senior Pharmacologist

Core Classification Acceptable

Summary
4 adult male humans dosed dermally at 6.7 ug/cm^2 for 24 hours, washed and followed to 168 hours. 5.64% absorbed. 6 adult male humans dosed dermally at 79 ug/cm^2 for 24 hours, washed and followed to 168 hours. 1.18% absorbed.

Materals

Atrazine U-ring-^{14}C-atrazine
Low dose
chemical purity 94.3%
radiochemical purity 98.4%
specific activity 38.7 uCi/mg
High dose
chemical purity 96.3%
radiochemical purity 98.0%
specific activity 12.8 uCi/mg
from Ciba-Geigy

Formulation blank
Atrazine AATREX-4L formulation
from Ciba-Geigy

Experimental design

Adult male human volunteers were dosed as follows;

Group	Number Subjects	Target Atrazine Dose mg	Target Atrazine Dose ug/cm^2	Dose Volume ul/25 cm^2	Total Activity uCi	Specific Activity uCi/mg
A	4	0.2	8	100	10	38.7
B	6	2.0	80	100	25	12.8

Group A was designed to assess absorption at the field exposure dose and group B to allow determination of urinary metabolites.

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Dose preparation

"The dose formulations were prepared by the sponsor. The low dose of [^{14}C]-Atrazine AATREX-4L formulation (Code No. CL-XXXVIII-31) was prepared by throughly mixing 20 mg of [^{14}C]-Atrazine (GAN-XXXV-62) and 28 ml of 4L blank formulant, and suspending the mixture in 10 ml of deionized water. The high dose of [^{14}C]-Atrazine AATREX-4L formulation (Code No. CL-XXXVIII-30) was prepared by throughly mixing 100 mg of [^{14}C]-Atrazine (GAN-XXXV-63) and 140 ml of 4L blank formulant, and suspending the mixture in 5 ml of deionized water."

"Stability of the dosing forumlations was determined by the sponsor before and after dosing."

"Triplicate aliquits of diluted formulation (0.1g) were analysed to determine the concentrations of ^{14}C in the formulation. This was done two days after receipt, prior to administration and the day after last administration."

Dosing Procedure

"A 25 square centimeter area, 2.0 cm by 12.5 cm was marked on the left ventral forearm of each volunteer. The marked area received a single topical application of [^{14}C]-Atrazine dose formulation delivered with a 0.1 ml Teflon coated syringe (Hamilton Company, Reno Nevada 89520-0012). The delivered dose was quantitated by weighing the microsyringe before and after dosing."

"After topical application, the dosed area was allowed to air dry. A non-occlusive plastic cover was then secured over the dosed area and kept in the place by tape for 24 hours. The cover was shaped as a half round cylinder with dimensions of 15 cm x 5 cm by 2.5 cm (length x width x height). This allowed free movement of air from its two open sides and the three holes on the top. The volunteers were requested not to touch or wash the dosed area for 24 hours."

Skin washing and skin stripping

"Twenty-four hours after dosing, the cover was removed and the dosed site was washed using gauze pads (Sherwood Medical S. Louis MO), Ivory liquid soap (Proctor and Gamble, Cincinatti, OH) and water."

"The tape stripping was done 168 hours after skin washing[1]. The dosed skin site was stripped with cellophane tape (3M Commercial Office Supply Division, St Paul MN) 10 times."

1. Typographical error should be '168 hours after dosing'.

Urine and fecal samples

"Urine samples were collected one hour before dosing and 0-4, 4-8, 8-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 hours after dosing."

"Fecal samples were collected one hour before dosing and 0-24, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 hours after dosing."

Samples analysed

The following samples were analysed;

skin wash
cover wash
stripping
urine (each collection period)
feces (each collection period)

Results

Table A. Atrazine hunan dermal absorption. Summary of mean percent dose distribution. MRID 439344-09

Skin wash	Tape strip	Cover Wash	Total Urine	Total Feces	Absorbed[1]	Total Recovered
Group A (6.7 ug/cm^2) 4 subjects						
95.37	0.0039	0.149	5.03	0.61	5.64	101.16
Group B (79 ug/cm^2) 6 subjects						
91.12	0.0006	0.060	1.11	0.07	1.18	92.36

1. sum af urine and fecal excretion

Table B. Atrazine hunan dermal absorption. Percent excretion. MRID 439344-09

Sample (hrs)	Group A (6.7 ug/cm^2) 4 subjects				Group B (79 ug/cm^2) 6 subjects			
	Urine		feces		Urine		feces	
	mean	cumulative	mean	cumulative	mean	cumulative	mean	cumulative
0-4	0.0045	0.0045	-	-	0.0353	0.0353	-	-
4-8	0.0967	0.1011	-	-	0.0649	0.1002	-	-
8-12	0.5041	0.6052	-	-	0.0951	0.1953	-	-
12-24	0.5272	1.1325	0.0193	0.0139	0.2212	0.4165	0.0121	0.0121
24-48	2.2405	3.3729	0.1379	0.1572	0.2869	0.7033	0.0189	0.0311
48-72	0.8839	4.2568	0.1672	0.3244	0.1935	0.8967	0.0138	0.0449
72-96	0.4317	4.6885	0.1046	0.4290	0.0962	0.9929	0.0216	0.0665
96-120	0.2055	4.8940	0.0796	0.5086	0.0631	1.0561	0.0018	0.0683
120-144	0.0939	4.9879	0.0292	0.5378	0.0262	1.0822	0.0031	0.0714
144-168	0.0300	5.0270	0.0989	0.6064	0.265	1.1087	0.0004	0.0718

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Data Evaluation Report

Chemical Atrazine

Citation

Intrim report. In vivo percutaneous absorption of atrazine in man. H.I. Maibach. Ciba NC. ABR-96003 Jan 29, 1995. MRID 439344-10

Reviewed by

10/31/96

Robert P. Zendzian Ph.D.
Senior Pharmacologist

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