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OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

1/14/2000

MEMORANDUM

SUBJECT: Dermal absorption of diazinon in humans — D264470
PC 057801

TO: Jess Roland PhD
Chief
Reregistration Br 3
Health Effects Division (7509C)

1/11/00

FROM: Robert P Zendzian PhD
Senior Pharmacologist
Science Evaluation Br
Health Effects Division (7509C)

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

1/14/2000

Action Requested

Review the following dermal absorption study of diazinon in humans.

Citation
In vivo percutaneous absorption of Diazinon in man. Wester, R. C. Surge laboratory Dept. of Dermatology, UCSF. Study nos S719, S817, S818, S820, S821, S822, S823, S824, S815 & S816 Aug 31,1999. MRID 44982801

Core Classification Acceptable/nonguideline

Summary
Six adult male human volunteers per group were dosed dermally with 14C-Diazinon. The application site was washed with soap and water after 24 hours and tape stripped after 7 days. Total urine was collected for 7 days and analyzed for radiolabel. Five rhesus monkeys were dosed intravenously with 14C-Diazinon and total urine and feces collected for 7 days. Urine and feces were analyzed for radiolabel. Rhesus urinary excretion of radiolabel (56%) was used to correct human urinary excretion of radiolabel as a measure of absorbed dose. Dose distribution

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was as follows:

Group /dose	Application Site	Formulation Vehicle	Skin Wash %	Tape Strip %	Urine %	Total Recovery %	Absorbed[a] %
A 2ug/cm^2	Ventral forearm	Acetone	0.4566	0.0096	1.9983	2.4645	3.5584
B 2ug/cm^2	Abdomen	Acetone	1.4448	0.0060	1.8095	1.9603	3.2313
C 1.47ug/cm^2	Abdomen	Lanolin	0.3543	0.0421	1.2757	1.6721	2.2780

a. From urinary excretion corrected by iv rhesus urinary excretion (56%).

Recommendations

1. The human dermal absorption values should not be used for oral to dermal conversion in risk assessment.
2. The default value of 100% dermal absorption (equal oral and dermal toxicity) should be used for oral to dermal conversion in risk assessment.
3. The Registrant may wish to perform a subchronic dermal toxicity study in the rat in order to determine effect and no effect levels for direct use in dermal risk assessment.

Discussion

As noted in the DER, total recovery in this study was very low, 2.5, 2.0 and 1.7 5% of the applied doses. This is a function of the experimental design which made no attempt to protect the application site to either collect volatile material or to protect against loss of test chemical to clothing in contact with the site. This may be considered a deficiency of the study or it may be considered as having made the study more realistic. No judgement will be made on this matter at this time.

Urinary excretion of label was corrected by using data from an intravenous study in the monkey where 56% of the label was excreted in the urine. Use of a related primate species rather than the human subjects may be questioned but considering the high percent of urinary recovery it will not be expected to make a significant difference.

Use of acetone and lanolin as solvents may also be questioned. Acetone can be expected to over estimate absorption and over estimate the risk. Lanolin was used in the study to quantitate the effects of different solvents. It shows a small quantitative difference but a relatively large percent difference. None of this effects our risk assessment if we use the acetone data for risk assessment.

However, there is another overriding reason not to use the dermal absorption data for risk assessment, the relative oral and dermal toxicity of diazinon. If one were to use the highest dermal absorption rate obtained in the study (3.6%) to convert an oral dose to a dermal dose for a

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particular toxic effect one would be using a conversion factor of 27.8. That is, one would expect the equitoxic dermal dose to be 27.8 times the oral dose. Available animal data do not agree with this conversion value.

Gaines (1969) tested two samples of diazinon for acute oral and dermal lethality in male rats with the following results:

LD_{50} mg/kg	Oral	Dermal	Ratio Dermal/Oral
sample 1	108	200	1.85
sample 2	250	900	3.60

Also, deaths were observed at 100 mg/kg/day (9/22 females) in an oral rabbit teratology study dosed day 6 through 18 and at 100 mg/kg/day after five doses (4/5 males) in a 21-day dermal rabbit toxicity study indicating similar toxicity by both routes.

There are a large number of factors which can account for these differences but we lack the information necessary to quantitatively or even qualitatively evaluate/explain them. At this point we can only note that the differences between oral and dermal toxicity of a chemical are not solely due to differences in route related absorption and that these differences may be only a minor factor in the route related toxicity of a particular chemical.

Reference

Gaines, T.B. Acute Toxicityof pesticides. Toxicol and Applied Pharmacol 14No. 3 May 1969 515-534

Data Evaluation Report 014058

Chemical Diazinon

Study type Dermal absorption in humans

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In vivo percutaneous absorption of Diazinon in man. Wester, R. C. Surge laboratory Dept. of Dermatology, UCSF. Study nos S719, S817, S818, S820, S821, S822, S823, S824, S815 & S816 Aug 31,1999. MRID 44982801

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a. Corrected by iv rhesus urinary excretion

The following is abstracted from the study report

5. MATERIALS

5.1 Test Article and Dose Formulation

[14C]-Diazinon (0.066 mCi/mg) was supplied by Ciba Geigy, Basel, Switzerland.

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The lanolin wool grease was prepared and provided by the sponsor. The wool grease was prepared from wool known to be free of pesticides. The wool was extracted with both heptane and then isopropranol so that the grease contained both polar and non-polar components.

Dose formulations were prepared fresh in the laboratory prior to use.

5.2 Measurement of Radioactivity of Formulations

An aliquot was taken from all dose formulations prior to treatment and analyzed for radioactivity content.

4. STUDY DESIGN

Diazinon was applied to the skin in either a standard acetone formulation or formulated in lanolin wool grease. Skin application sites were the forearm and abdomen, both relevant skin exposure areas (Wester and Maibach, 1989). Urinary excretion of 14C was determined. To determine bioavailability, rhesus monkeys were intravenously administered 14C-Diazinon in propylene glycol and urinary and fecal ^{14}C excretion was determined (Wester et al. 1992, 1993, 1998).

4.1 Human Volunteers

The study was divided into 3 groups:

Group	Application Site	Formulation Vehicle	Target Diazinon Dose		Volume	Specific Activity
			ug	ug/cm^2	ug/l0cm^2	uCi/mg
A	Ventral forearm	Acetone	20	2	50	66
B	Abdomen	Acetone	20	2	50	66
C	Abdomen	Lanolin	14.7	1.47	50	66

After treatment, the volunteers were informed not to wash the application site for 24 hours. The volunteers were allowed to wear their normal clothing and participate in their normal activities. Volunteers were instructed to collect all of their voided urine in the containers provided.

4.2 Rhesus Monkeys

Four female monkeys were administered 2.1 uCi ["C]-Diazinon in propylene glycol intravenously and their urine and feces collected for 7 days to determine the extent of 14C excretion.

5.3 Test Subjects

5.3.1. Human Volunteers

Human volunteers were recruited from the University of California, San Francisco Bay Area community. Eighteen normal, healthy males from ages 19 to 65 years old were selected for this study. The volunteers were free from significant cardiac, hepatic, renal, pulmonary, gastrointestinal, neurological, hematological and dermatologic disease as determined by medical history. The study was approved by the UCSF Committee on Human Research and each volunteer signed a consent form. Six volunteers were assigned to each group.

7.1.2 Rhesus Monkeys

Four female rhesus monkeys from the Surge Laboratory colony were used for the study. Their husbandry and health were maintained by UCSF Veterinary Staff.

6. DOSING, SAMPLING AND ANALYSIS

6.1 Dosing Procedure

6.1.1 Human Volunteers

A 10 cm^2 skin area was marked on the ventral forearm or abdomen of each volunteer. A single topical application of [14C]-Diazinon was applied to the area with a blunt syringe. An equal dose volume was delivered directly into a scintillation vial and the vial assayed for radioactivity in oral to quantitate the dose.

6.1.2 Rhesus Monkeys

A single dose containing 2.1 [,Ci [14C]-Diazinon in propylene glycol was administered intravenously via the saphenous vein of each monkey.

6.2 Skin Washing and Analysis (Human)

After 24 hours, the skin application sites were washed with 50% liquid Ivory soap (1/1,v/v) and water. The radioactivity in the cotton balls from the washing of the site of application was individually counted in 16 ml of scintillation cocktail with the liquid scintillation spectrophotometer.

6.3 Skin Tape Stripping and Analysis (Human)

Tape stripping was done 168 hours after application. The treated skin site was stripped

with cellophane tape (3M Commercial Office Supply Division, St. Paul, MN) 10 times. These tapes were then individually placed in borosilicate glass vials with 16 ml of scintillation cocktail and subsequently assayed for radioactivity by liquid scintillation counting.

6.4 Urine Sample Collection and Analysis (Human and Rhesus)

Urine samples were collected 0 - 24, 24 - 48, 48 - 72, 72 - 96, 96 - 120, 120 - 144, and 144 - 168 hours after dosing. Urine volumes were measured and an aliquot of each sample was stored refrigerated until analysis. Samples were analyzed in duplicate for 14C . A 5 ml aliquot of each urine sample was assayed in 10 ml of scintillation cocktail (Universal ES, Costa Mesa, CA) and radioactivity was measured by liquid scintillation counting.

6.5 Feces Sample Collection and Analysis (Rhesus)

Feces samples were collected 0 - 24, 24 - 48, 48 - 72, 72 - 96, 96 - 120, 120 - 144, and 144 - 168 hours after treatment. Duplicate aliquots of the 24-hour samples were placed in a centrifuge tube and homogenized. The aliquots of the fecal homogenate (0.2 g) were combusted. Radioactivity of the sample was then measured by liquid scintillation counting.

6.6 Scintillation Counting

All radioactivity measurements were conducted using a Model 4640 Liquid Scintillation Counter (Packard Instruments). The counter was calibrated using sealed samples of quenched and unquenched standards as detailed by the instrument manual. Background control and test samples were counted in duplicate where possible. Aliquots of urine, skin wash, and tape strip samples were mixed directly with Universal Scintillation Cocktail (ICN Biomedicals, Costa Mesa, CA) and analyzed for radioactivity. Aliquots of feces homogenate samples were oxidized in a Packard Oxidizer. The collected [14C]-CO^2 was analyzed for radioactivity by liquid scintillation counting.

6.7 Data Analysis

Urinary 14 C excretion following topical application 4 of [14 Cl-Diazinon was determined in the human volunteers. Urinary 1 C excretion following intravenous administration of [14C]-Diazinon was determined in rhesus monkeys. An intravenous dose is 100% bioavailable (injected into body) and provides a means of accounting for Diazinon which would be excreted by some other route or retained in the body when treatment by topical application is utilized.

Therefore, percutaneous absorption of Diazinon in humans was determined from the

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following equation:

Percent dose absorbed = $\frac{\text{Human urinary 14C excretion (topical administration)}}{\text{Monkey urinary 14 C excretion (i.v. administration)}}$ = x 100

Control and test sample counts were corrected by subtracting 1 X background radioactivity using Appleworks/Apple IIE computer, Apple Computer Co., Mountain View, CA. Data were tabulated and half-lives were calculated from log percent radioactivity remaining in urine to be excreted (U--U).

End of abstract

Results

Results of the study are summarized in Tables 1,2 and 3 human dermal dosing and 4 monkey intravenous dosing.

Percent recovery in the human studies was as shown below. Percent absorbed was calculated by dividing the percent excreted in the human urine by the percent excreted in the monkey urine following the intravenous dose (56%) as noted in the exuation above..

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A 2ug/cm^2	Ventral forearm	Acetone	0.4566	0.0096	1.9983	2.4645	3.5584
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Discussion

Total recovery in this study was very low, 2.5, 2.0 and 1.7 5% of the applied doses. This is a function of the experimental design which made no attempt to protect the application site to either collect volatile material or to protect against loss of test chemical to clothing in contact with the site. This may be considered a deficiency of the study or it may be considered as having made the study more realistic. No judgement will be made on this matter at this time.

Urinary excretion of label was corrected by using data from an intravenous study in the monkey

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where 56% of the label was excreted in the urine. Use of a related primate species rather than the human subjects may be questioned but considering the high percent of urinary recovery it will not be expected to make a significant difference.

Use of acetone and lanolin as solvents may also be quentioned. Acetone can be expected to over estimate absorption and over estimate the risk. Lanolin was used in the study to quantitate the effects of different solvents. It shows a small quantitative difference but a relatively large percent difference. None of this effects our risk assessment if we use the acetone data for risk assessment

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Table 1. Percent distribution of Dose for Human Volunteers following Application to Forearm in Acetone Vehicle. Data from tables 1, 4 and 7 of the report

Volunteer #1	Volunteer #2	Volunteer #3	Volunteer #4	Volunteer #5	Volunteer #6	Mean	S.D.
Mean total skin wash							
1.2421	0.5196	0.6676	0.1112	0.1772	0.022	0.4566	0.4586
Mean total tape strip							
0.0086	0.0238	0.0122	0.0075	0.0039	0.0016	0.0096	0.0079
Mean total urine excretion							
0.4462	3.4041	1.0089	2.5238	2.8804	1.7263	1.9983	1.1395
Percent absorption from urine excretion corrected by mean monkey iv urine excretion 56%							
0.7967	6.0788	1.8016	4.5068	5.1436	3.0827	**3.5584**	N/A

Table 2. Percent Distribution of Dose for Human Volunteers Following Application to Abdomen in Acetone Vehicle. Data from tables 2, 5 and 8 of the report

Volunteer #1	Volunteer #2	Volunteer #3	Volunteer #4	Volunteer #5	Volunteer #6	Mean	S.D.
Mean total skin wash							
0.6247	7.3487	0.3705	0.1129	0.0783	0.1369	1.4448	2.8998
Mean total tape strip sample							
0.0047	0.0041	0.022	0.0013	0.0016	0.0021	0.0060	0.0080
Mean total urine excretion							
2.0193	2.6647	1.7261	3.2485	0.3462	0.8520	1.8095	1.0873
Percent absorption from urine excretion corrected by mean monkey iv urine excretion 56%							
3.6059	4.7584	3.0823	5.8009	0.6182	1.5214	**3.2313**	N/A

Table 3. Percent Distribution of Dose for Human Volunteers Following Application to Abdomen in Lanolin Vehicle. Data from tables 3, 6 and 9 of the report.

Volunteer #1	Volunteer #2	Volunteer #3	Volunteer #4	Volunteer #5	Volunteer #6	Mean	S.D.
Mean total skin wash							
0.2868	0.2973	0.2921	0.0164	1.1686	0.0644	0.3543	0.4178
Mean total tape strip							
0.0195	0.1249	0.0525	0.0122	0.0258	0.0174	0.0421	0.0430
Mean total urine excretion							
1.2910	0.9565	1.2702	1.2426	1.5828	1.3110	1.2757	0.1994
Percent absorption from urine excretion corrected by mean monkey iv urine excretion 56%							
2.3054	1.7080	2.2682	2.2189	2.8264	2.3411	**2.2780**	N/A

Table 4. Summary of Excretion Expressed as Percent of Administered Dose for Monkeys Following Intravenous Administration. Data from tables 13 and 14 of the report.

Animal #1	Animal #2	Animal #3	Animal #4	Mean	S.D.
Mean total urine excretion					
50.5850	61.6614	60.3000	50.6368	**55.7958**	6.0128
Mean total fecal excretion					
22.3486	16,6635	22.0597	29.2976	22.5924	5.1786