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

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MEMORANDUM

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

TO: R. J. Taylor/V. Walters,
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Registration Division (TS-767)

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Hazard Evaluation Division (TS-769)

Budd 3/24/83

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Toxicology Branch
Hazard Evaluation Division (TS-769)

SUBJECT: Study Entitled "Human Percutaneous Absorption of Paraquat", Conducted for Chevron Chemical Company by Howard I. Maibach, M.D., University of California Medical Center, San Francisco; September 24, 1982. EPA Accession No. 249511, EPA Record No. 91977. TOX Chem No. 634

This submission consists of 4 individual studies: one study with Rhesus monkeys in which urinary excretion of the injected (i.m.) ^{14}C-paraquat dichloride was studied; and three studies with adult human males in which the dermal absorption of ^{14}C-paraquat dichloride was investigated. Dermal absorption was determined by measuring total radioactivity in urine.

Monkeys eliminated 58.6% of the administered radioactivity in urine within 7 days after dosing. Most of this radioactivity was excreted within the first 24 hours after dosing.

Dermal absorption of ^{14}C-paraquat dichloride by human males was very low. Only 0.230, 0.285 and 0.295% of the applied dose was absorbed through the skin of their hands, legs and forearms, respectively, during 5 days after dosing.

The study with monkeys was evaluated separately by Toxicology Branch/HED. Because the only difference in conducting of the three dermal absorption studies was an application site, these studies were evaluated together.

Due to insufficient experimental details, each study was classified as Acceptable as Supplementary. There are no core criteria for these types of studies.

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OPP:HED:TOX:K.LOCKE:sb 3/22/83 X71511 Rm 824 #m23

Study Type: Metabolism

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Accession Number: 249511

Sponsor: Chevron Chemical Company

Contracting Lab: Howard I. Maibach, M.D.
University of California Medical Center
San Francisco 94143

Date: September 24, 1982

Test Material: ^{14}C-Paraquat Dichloride

Protocol:

Single doses of ^{14}C-paraquat dichloride (4.72 uCi equivalent to 607 ug; Specific Activity = 2 mCi/mM; MW 272.2) were injected intramuscularly into the thighs of 4 adult, male Rhesus monkeys. Urine samples were collected daily for 7 days and assayed for ^{14}C, using an internal standard and a liquid scintilation spectrophotometer. The first sample was assayed 24 hours after dosing.

Nothing was reported about the radiopurity of the test material and where it was labeled (in the methyl groups or in the ring); about the housing and feeding of the animals; and about the collection, storage and preservation of urine before the analyses.

There is also an error in the Procedures section of the submitted report. According to the author, a stock solution contained 2.4 ug of paraquat ion/ml. If this were correct, then a 0.25 ml dose would have contained 6.44 uCi of paraquat dichloride and not 4.72 uCi, as was reported by the author. A dose of 4.67 uCi (which is close to 4.72 uCi) can only be obtained if a stock solution contained 2.4 mg of paraquat dichloride/ml . (Calculations are attached.)

Results:

Most of the radioactivity (43.5-51.5% of the administered dose; average: 47.0%) was excreted between 0 and 24 hours after dosing. The excretion varied from 2.7% to 10% (average: 5.2%) of the administered dose on day 2 and only 0.5-1.0% of the dose (average: 0.7%) was excreted on day 7 following treatment with ^{14}C-paraquat dichloride. The total urinary excretion of the radioactivity during the 7-day period was 52.3%-72.3% (average: 58.6 $\pm$ 9.4%) of the injected dose. No attempt was made to characterize the radioactivity detected in urine.

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Conclusions:

Adult, male Rhesus monkeys excreted in urine 47% of the injected radioactivity during the first 24 hours after exposure. An additional 11% of the radioactive dose was eliminated in urine during the remaining 6 days of the study. The radioactivity was administered i.m. as single doses of ^{14}C-paraquat dichloride.

Because many experimental details are missing, as was already indicated in the Protocol section, it is difficult to conclude whether this study was carelessly conducted or just carelessly reported.

Classification of the Study: Acceptable as Supplementary (there are no core criteria for this type of a study).

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Study with workers

The stock solution must have contained 2.4 mg of ^{14}C-paraquat dichloride (and not ^{14}C-paraquat ion) / ml.

① It was reported that 0.25 ml of the stock solution (2.4 mg of paraquat ion / ml.) yielded 4.72 μCi as paraquat dichloride.

MW of paraquat dichloride 257.2 ; MW of paraquat ion 186.3

$$\frac{2.4 \text{ mg par. ion}}{\text{ml}} \times \frac{257.2}{186.3} = 3.313 \text{ mg paraquat } Cl_2 \text{ / ml of the stock solution}$$

0.25 ml × 3.313 mg par. Cl_2 / ml = 0.828 mg par. Cl_2 (dose injected)

Specific Activity (SA) of the stock solution: 2 μCi / μM or 2 mCi / mM

1 mM of paraquat dichloride = 257.2 mg

$$\frac{2.0 \text{ mCi}}{257.2 \text{ mg par. } Cl_2} = \frac{0.007776 \text{ mCi}}{\text{mg par. } Cl_2} = \frac{7.776 \text{ μCi}}{\text{mg par. } Cl_2}$$

Therefore, 0.828 mg par. Cl_2 × 7.776 μCi = 6.44 μCi (dose injected if the stock solution contained 2.4 mg par. ion / ml).

② Assuming that the stock solution contained 2.4 mg of paraquat dichloride / ml, then 0.25 ml × 2.4 mg / ml = 0.6 mg (dose injected as paraquat dichloride).

Then, $0.6 \text{ mg par. } Cl_2 \times \frac{7.776 \text{ μCi}}{\text{mg par. } Cl_2} = 4.67$ μCi (dose injected), which is closer to the reported 4.72 μCi than to the 6.44 μCi (calculated above).

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③ Dose of paraquat dichloride injected (in μg), calculated from the reported 4.72 μCi.

MW of paraquat dichloride 257.2 ; therefore, 1 μM = 257.2 μg
SA = 2.0 mCi/mM or 2.0 μCi/μM

$$\frac{4.72\ \mu Ci}{2.0\ \mu Ci} \times 1.0\ \mu M = 2.36\ \mu M \text{ (dose injected)}$$

$$2.36\ \mu M \times 257.2\ \mu g/\mu M = \underline{607\ \mu g} \text{ (injected dose as paraquat dichloride)}$$

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Study Type: Acute Dermal Absorption

Accession Number: 249511

Sponsor: Chevron Chemical Company

Contracting Lab: Howard I. Maibach, M.D.
University of California Medical Center
San Francisco 94143

Date: September 24, 1982

Test Material: ^{14}C-Paraquat Dichloride

Protocol:

Single doses of paraquat dichloride (Specific Activity = 2 mCi/mM; MW 272.2) were applied on the forearms (4.95 uCi), back of the hands (4.70 uCi) and back of the lower legs (5.33 uCi) of 6 healthy, adult male volunteers aged 18 years or older. Each application was made over a 70 cm^2 area, using 9 ug of paraquat dichloride/cm^2.* Volunteers were instructed not to wash the application sites for 24 hours following each application. Urine samples were collected at 4, 8 and 12 hours during the first day and then every 24 hours for a total of 5 days . The radioactivity was assayed with a liquid scintillation spectrophotometer, using a ^{14}C internal standard and a triplicate vial of each sample. Only polystyrene or polypropylene laboratory apparatus was used in this study (paraquat adsorbs to untreated glass). Each application site represented a separate experiment.

The following experimental details were not reported:

1. Radiopurity of ^{14}C-paraquat dichloride and where it was labeled (in the methyl groups or in the ring).

2. Who were these volunteers? Were they university students, faculty members and/or hospital staff?

3. How old was each volunteer?

4. Where did they live during the 5-day test period? At home or at the Medical Center?

5. How was the urine preserved and stored before the analysis for ^{14}C?

6. Were the application sites covered during the 24-hour exposure period?

* There is an error in the Procedures section of the submitted report. According to the author, a stock solution used contained 2.4 mg of paraquat ion/ml. If this were correct, then each application would have contained 11.83 ug of paraquat dichloride/cm^2 and not 9 ug/cm^2, as was reported by the author. A stock solution contained, therefore, 2.4 mg of paraquat dicholoride (and not paraquat ion)/ml.

Each 0.25 ml of the same stock solution (volume of a dose), applied on the skin, contained a different number of uCi indicating that the stock solution was being concentrated (due to evaporation of water). The actual numbers of uCi of ^{14}C-paraquat dichloride applied/cm^2 were as follows: forearm (9.09), hand (8.63) and legs (9.79). Calculations are attached.

Results:

Dermal absorption of ^{14}C-paraquat dichloride by adult, human males was determined by measuring the total amount of ^{14}C excreted in the urine. Each calculated value was then corrected for imcomplete urinary excretion, using data from the study with four Rhesus monkeys where 58.6% of the administered (i.m.) ^{14}C-paraquat dichloride was eliminated in urine.

Irrespective of the site of application, the absorption of paraquat dichloride through the skin was very low. With all application sites, the peak excretion of ^{14}C in urine occurred between 0 and 24 hours after dosing, when data are expressed as a plot of the percent of the dose excreted/hour versus time. However, inspection of Tables dated 8/16/82, 8/30/82 and 9/13/82 shows that there were wide variations in the amount of urinary ^{14}C for the same subject and among subjects, for all application sites. These data are summarized below.

Site of Application	Urinary Excretion of ^{14}C (%)*		
	Average	SD**	Range
Forearm	0.293	0.117	0.205-0.519
Back of Hand	0.230	0.078	0.123-0.341
Lower Leg	0.285	0.232	0.052-0.702

* Of the applied dose ** Standard Deviation

Insufficient experimental details preclude further comments on this study.

Conclusion:

^{14}C-Paraquat dichloride, applied on the forearms, hands and lower legs of 6 adult human males, was absorbed very poorly. Dermal absorption of the test material was measured by monitoring urinary excretion of ^{14}C for a total of 5 days after dosing.

Classification of the Study: Acceptable as Supplementary (there are no core criteria for this type of a study).

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OPP:HED:TOX:K.LOCKE:sb 3/21/83 X71511 Rm 824 #m24

Study with human males 002620

① It was reported that 0.25 ml of the stock solution (2.4 mg of paraquat ion / ml), applied over 70 cm^2 area, equaled 9 µg of paraquat dichloride / cm^2, but this is incorrect.

MW of paraquat dichloride 257.2
MW of paraquat ion 186.3

$2.4 \text{ mg par. ion / ml} \times \frac{257.2}{186.3} = 3.313 \text{ mg of paraquat dichloride / ml}$

0.25 ml × 3.313 mg / ml = 0.828 mg = 828 µg of paraquat dichloride (dose applied over 70 cm^2 of the skin on hands, legs or forearms).

$\frac{828 \text{ µg}}{70 \text{ cm}^2} = \underline{11.83 \text{ µg / cm}^2}$, and not 9 µg / cm^2, as was reported.

② Assuming that the stock solution contained 2.4 mg of paraquat dichloride / ml, then 0.24 mg / ml × 0.25 ml = = 0.6 mg = 600 µg was applied over 70 cm^2 area.

600 µg / 70 cm^2 = 8.6 µg / cm^2, which is closer to the reported 9 µg / cm^2 (≈ 4.5 % error) than to the calculated (above) 11.83 µg / cm^2.

③ It was reported that 0.25 ml of the stock solution yielded the following doses of paraquat dichloride: 4.70 µCi (applied on hand), 4.95 µCi (applied on forearm) and 5.33 µCi (applied on leg). Each dose equaled, presumably, 9 µg of paraquat dichloride / cm^2.

Each application site represented a separate study and the interval between studies was about 2 weeks. (Tables summarizing results for hands, forearms and legs are dated 8/16/82, 8/30/82 and 9/13/82, respectively). Because the same dose (0.25 ml) contained more microcuries with time, the stock solution was apparently being concentrated (due to evaporation of water). The actual number of micrograms of paraquat dichloride / cm^2 was, therefore, as follows:

HAND

SA of paraquat dichloride = 2.0 m Ci / mM = 2.0 m Ci / 257.2 mg = 7.776 μCi / mg

4.70 μCi / 70 cm^2 = 0.0671 μCi / cm^2

$$\frac{0.0671\ \mu Ci/cm^2}{7.776\ \mu Ci/mg} = \frac{0.0671\ \mu Ci/cm^2}{7.776\ \mu Ci/1000\ \mu g} = \underline{8.63\ \mu g/cm^2}$$

FOREARM

4.95 μCi / 70 cm^2 = 0.0707 μCi / cm^2

$$\frac{0.0707\ \mu Ci/cm^2}{7.776\ \mu Ci/1000\ \mu g} = \underline{9.09\ \mu g/cm^2}$$

LEG

5.33 μCi / 70 cm^2 = 0.0761 μCi / cm^2

$$\frac{0.0761\ \mu Ci/cm^2}{7.776\ \mu Ci/1000\ \mu g} = \underline{9.79\ \mu g/cm^2}$$