5-25-88

Caswell

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

007556

MAY 25 1988

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Oxamyl: Review of A Dermal Absorption Study on Rats with Vydate (formulation of oxamyl)

Caswell No.: 561A EPA ID No.: 352-372
352-400

Record No.: 212525/121527

FROM: Whang Phang, Ph.D. 4/26/88
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TO: Dennis Edwards, PM (12)
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THROUGH: Marcia van Gemert, Ph.D. 4/26/88
Head, Section III
and
William Burnam
Deputy Branch Chief
Toxicology Branch/HED (TS-769c)

The registrant, E. I. Du Pont de Nemours & Co., has submitted a dermal absorption study on oxamyl in male Sprague Dawley rats. The data evaluation report for this study is attached, and the conclusion is as follows:

Groups of 6 male Sprague-Dawley rats were applied oxamyl at concentrations of 48.0 and 5.4 mg/200 ul on a 4 x 6 cm of shaved skin on the upper back. The following observations were obtained:

1). Limited data indicated that oxamyl was slowly absorbed through skin.

2). Urinary route is the major route of excretion for oxamyl.

3). Much of the test compound remained in the gauze which covered the application site.

The use of gauze to cover the application site is considered as an unacceptable practice because the gauze will absorb most of the applied chemical. The actually amount of the test chemical available for absorption can not be accurately quantified. This is a major experimental defect, and the study is classified as an Unacceptable study.

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Reviewed by: Whang Phang, Ph.D. 4/26/88
Section , Tox. Branch (TS-769C)
Secondary reviewer: Marcia van Gemert, Ph.D. 4/26/88
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DATA EVALUATION REPORT

STUDY TYPE: Dermal Absorption-Rat TOX. CHEM. No.: 561A

ACCESSION No.: 403701-01 RECORD No.: 212525/212527

EPA ID No.: 352-372/352-400 PROJECT No.: 8-0576

TEST MATERIAL: Radiolabelled oxamyl in Vydate®L
Two solutions: 1). 49 mg oxamyl/200 uL
2). 5.5 mg oxamyl/200 uL

TESTING FACILITY: Battelle, Columbus, Ohio

SPONSOR: E.I. du Pont de Nemours & Co., Inc.

CITATION: Johnson, J.D., Chinn, J.W., and Kluwe, W.M. Dermal Absorption of ^{14}C-Oxamyl in the Rat. Study No.: AMR-614-86; Laboratory Report No.: N07667400.; Battelle, Columbus, Ohio. Oct 6, 1986. Submitted by E.I. du Pont de Nemours & Co., Inc. Oct 13, 1987.

CONCLUSIONS:

Groups of 6 male Sprague-Dawley rats were applied oxamyl at concentrations of 48.0 and 5.4 mg/200 ul on a 4 x 6 cm of shaved skin on the upper back. The following observations were obatined:

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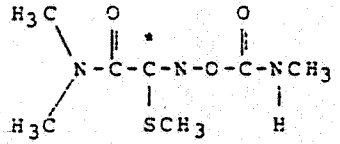
Materials and Methods:

Test compound:



* location of ^{14}C label

Purified ^{14}C-oxamyl (99.3% pure; specific activity, 5.6 uCi/mg) was add to other ingredients to obtain a formulation equivalent to commercial Vydate*L. From this stock other dosing solutions were prepared.

Solution No. 1 (high dose) was prepared by adding the stock solution to Du Pont Vydate® resulting in a solution containing 48.6 mg of oxamyl/200 ul (specific activity: 0.305 uCi/mg).

Solution No. 2 (low dose) was prepared by adding the stock solution to water yielding a solution 5.5 mg oxamyl/200 ul (specific activity: 2.57 uCi/mg).

Test Animal: 24 Sprague-Dawley male rats were obtained from Charles River Breeding Laboratories, Inc., Portage, Michigan. The weights of these animals ranged from 311 to 325 gm.

Experimental Design: The crucial points of the experimental design are summarized here, and the details are presented in the Appendix.

Two groups of 12 rats were designated to received either Solution No. 1 (48.6 mg/200 ul) or Solution No. 2 (5.53 mg/ul). Each group was subdivided into either blood sample study groups or excretion sample study groups each of which consisted of 6 rats as shown below:

Dose	Sample Study Group	No of Rats
Soln. No. 1 (48.6 mg/200 ul)	Blood	6
Soln. No. 1 (48.6 mg/200 uL)	excretion	6
Soln. No. 2 (5.53 mg/200 uL)	Blood	6
Soln. No. 2 (5.53 mg/200 uL)	excretion	6

If all six rats in each subgroup survived without any complications, then one rat from each group was randomly selected for exclusion from further analysis.

Dose Application: An area of approximately 5x7 cm on each rat's back, below the shoulder and along longitudinal axis of the body was shaved. An aliquot of 200 ul of the test agent was applied on a 4x6 cm shaved area. The application site was allowed to dry for approximately 20 min while the animal was manually restrained. Subsequently, the application site was covered with 2 layers of 10 x 10 cm cotton gauze which was wrapped over by an adhesive elastic dressing.

After 8 hours of dosing, all the dressing was removed and saved for radioactivity analysis. It should be noted that a green dye was added to the dosing solution to aid visualization of any transfer of the test agent to the gauze. The application site was thoroughly washed with a warm and mild Ivory soap solution, rinsed with warm water, and dried. This process was repeated 2 to 5 times untill no visible dosing solution was removed from the application site. Just prior to sacrifice, the application site skin was again washed with the detergent solution and a water rinse. All washes and swabs were saved for radioactivity analysis.

Sample Collection:

Blood: 400 ul of serial blood samples were collected at 0 (pre-dose), 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144, and 168 hours after dosing.

excretion: Urine and feces were collected during the following intervals after dosing: 0-6, 6-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144, and 144-168 hours. After 168 hours of collection, the rats were sacrificed. A cardiac blood sample (approximately 10 ml) was collected from each rat. The following tissues samples were collected for radioactivity analysis:

application site skin
non-application site skin (near the tail)
kidneys
liver
leg muscle
gastointestinal tract
carcass

Sample Analysis: The procedures for sample preparation and sample analysis are presented in the Appendix.

RESULTS

The radioactivity analysis of the dosing solution indicated that the mean of the radioactivity high dose was 14.8 uCi/200 ul, and that of low dose was 14.2 uCi/200 ul. The actual dose applied

doses were 46.0 and 5.4 mg for high and low dose, respectively.

Concentrations of radicactive oxamyl in blood were generally low (Table 1). For high dose animals, the blood level of oxamyl was below the detection level during most of the assaying intervals except at 36 or 48 hours for 4 rats. For low dose animals, the blood concentration of oxamyl was below the detection level for most of the measuring intervals earlier than 24 hours for 4/5 rats. One animal showed higher concentration of radioactive oxamyl between 12 and 48 hours than any other animals. In general, the peak concentrations of radioactive oxamyl in blood occurred long after the test compound was removed from the application site.

The data on urinary excretion of radioactive oxamyl are presented in Table 2. Maximum urinary excretion occurred from 6 to 24 hours for both high and low dose animals. The excretion continued till the end of the study, and significant amount of radioactivity was still being excreted at the end of the study. The mean of the total amount eliminated via urine was 2.24 and 3.34 % of the applied dose for high and low dose animals, respectively.

Table 3 shows the excretion of radioactive oxamyl in feces. The data indicated that a substantially less radioactivity was excreted via feces relative to that excreted in urine. The peak of excretion occurred during the 12 to 48 hour interval.

The radioactivity in tissues at 168 hours after dermal application was presented in Table 4. Carcass and skin application site of all treated animals contained the greatest amount of the radioactivity among all the tissues examined. The non-application site of the skin also contained a substantial amount of radioactivity. This finding was consistent with that seen in the previous metabolism study in rats with oral dosing.

The mean of total radioactive oxamyl equivalent in all tissues tested, excreted in urine and feces, and in carcass was termed total bioavailability which was expressed as percentage of the applied dose, and this set of data was presented in Table 5. The mean of total bioavailability or absorption was calculated to be 3.9% for high dose animals and 6.6% for low dose animals.

The total recovery of radioactivity is presented in Table 6. The data indicated that greater percentages of the applied dose were in the gauze and swabs. The calculated total recoveries of the radioactivity in this study were 102.7% for high dose group and 97.6% for low dose group.

DISCUSSION:

Groups of 6 male Sprague-Dawley rats were applied oxamyl at concentrations of 48.0 and 5.4 mg/200 ul on a 4 x 6 cm of shaved skin on the upper back. The following observations were obtained:

1). For most of the treated rats and at the majority of the sampling times, the blood concentration of radioactive oxamyl was either below or barely above the detection level. As a result this set of data was difficult to interpret. Nevertheless, the limited data implied that dermal absorption of radioactive oxamyl was slow under these experimental conditions.

2). Urinary and fecal excretion data indicated the primary route of excretion for dermally administered oxamyl in rats was via urine. This observation was consistent with that of a metabolism study in rats with oral route of administration.

The observation that a significant amount of radioactivity was still being eliminated at 168 hours after dosing indicated that oxamyl which remained in the skin was slowly being distributed from the skin application site.

3). Based upon the reported data the means of the total absorption of radioactive oxamyl expressed as percentage of the applied dose were 3.9% for high dose rats and 6.6% for low dose animals.

4). The data on the total recovery indicated that much of the applied ^{14}C-oxamyl remained in the gauze that covered the application site. Using the gauze to cover the application site would not be considered as an acceptable practice because a gauze often absorbed the test chemical and prevented it from being absorbed by the animal. As seen in Table 7 approximately 8% of the applied dose was found in the "digest" of the gauze, and this amount could not possibly be made available for absorption. In addition the actual amount of radioactive oxamyl available for absorption could not be properly quantitated.

The use of gauze to directly cover the application site is considered as a major defect for this study, and the study is classified as Unacceptable.

OXAMYL

Page _____ is not included in this copy.

Pages 7 through 20 are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

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_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

_____ A draft product label.

_____ The product confidential statement of formula.

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