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

CASWELL 112

010035

FEB 12 1993

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Oxamyl: Review of a metabolism study in rats

Caswell No.	561A	ID No.	103801
MRID No.	415208-01	EPA Case No.	819376
DP Barcode.	D179549	Submission No.	S419916

TO: Brigid Lowery/L. Schnaubelt, PM Team 72
Special Review and Registration Division (7508C)

FROM: Whang Phang, Ph.D. *Whyte*
Pharmacologist
Tox. Branch II/HED (H7509C) *2/2/93*

THROUGH: James Rowe, Ph.D. *James N. Rowe 2/2/93*
Section Head
&
Marcia van Gemert, Ph.D.
Branch Chief
Tox. Branch II/HED (H7509C)

The registrant, du Pont Agricultural Products, submitted a rat metabolism study on oxamyl. This study has been reviewed. A Data Evaluation Report (DER) of this study is attached, and the conclusion is as follows:

When 5 male and 5 female rats received a single oral dose of ¹⁴C-oxamyl (1 mg/kg), approximately 80% of the administered radioactivity was eliminated in the urine after 24 hrs of dosing, and approximately 91% of the dose was eliminated in the urine by 168 hrs. Less than 3% of the dose was found in the feces, and approximately 1% of the dose was found in the carcass. Except for muscle and skin, less than 1 % of the dose was found in any tissue examined. The data indicated that oxamyl was readily absorbed with oral administration and rapidly metabolized and eliminated in the urine. There was no sex difference in the patterns of elimination, and there was essentially no sequestration of oxamyl or its metabolites in any tissue examined.

Using oxime, which was a hydrolysis product of oxamyl and which had lower toxicity than oxamyl, the major metabolite of oxamyl was identified as β -glucuronide of the oxime. Based upon these findings, a major route of metabolism of oxamyl was proposed to be the hydrolysis of oxamyl to oxime which was then conjugated with glucuronide.

The results of this study provided sufficient information for the understanding of metabolism of oxamyl, and the study met the principal data requirements of a metabolism study (85-1). It is classified as **acceptable**.

Concerning the absence of a low-dose treatment and a repeated low-dose treatment in this study, the registrant requested a waiver for these two parts of the study on oxamyl. Tox. Branch II has reviewed the rationale presented by the registrant, all the relevant information on oxamyl, and the information on a related compound, methomyl. Based on this evaluation, Tox. Branch II has recommended that the request be granted for the reasons stated in a memorandum from W. Phang (Tox. Branch II/HED) to B. Lowery and L. Schaubelt (SRRD) (1/25/93).

Reviewer: Whang Phang, Ph.D. *Whang Phang 2/2/93*
Tox. Branch II/HED (H7509C)

Secondary Reviewer: Alberto Protzel, Ph.D. *Alberto Protzel 2/2/93*
Tox. Branch II/HED (H7509C)
James Rowe, Ph.D., Section Head
Tox. Branch II/HED (H7509C)

DATA EVALUATION REPORT

Study Type: Metabolism study in rats (high dose)

Chemical: Oxamyl; IND-1410-196

Caswell No.	561A	ID No.	103801
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Sponsor: E. I. du Pont de Nemours and Co.

Testing Facility: Huntingdon Research Centre, Ltd., England.

Citation: Hawkins, D. R., Mayo, B. C., Pollard, A.D., Haynes, L., and Donschak, W.W. (1990) Biokinetics and metabolism of ¹⁴C-oxamyl in rats. Unpublished study by Huntingdon Research Centre, Ltd.; Study No. AMR-1226-88. (June 5, 1990). Submitted to EPA by DuPont Agricultural Products. EPA MRID No. 415208-01.

Conclusion: When 5 male and 5 female rats received a single oral dose of ¹⁴C-oxamyl (1 mg/kg), approximately 80% of the administered radioactivity was eliminated in the urine after 24 hrs of dosing, and approximately 91% of the dose was eliminated in the urine by 168 hrs. Less than 3% of the dose was found in the feces, and approximately 1% of the dose was found in the carcass. Except for muscle and skin, less than 1 % of the dose was found in any tissue examined. The data indicated that oxamyl was readily absorbed with oral administration and rapidly metabolized and eliminated in the urine. There was no sex difference in the patterns of elimination, and there was essentially no sequestration of oxamyl or its metabolites in any tissue examined.

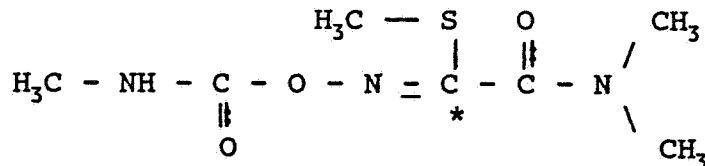
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Methods and Materials:

Test article: Radiolabeled oxamyl: Batch No., E52467-29; specific activity, 85 $\mu\text{Ci}/\text{mg}$; adjusted to 90473 dpm/ μg for dosing; radiochemical purity, approximately 98%. The location of radiolabel on oxamyl is indicated by * as follows:



Radiolabeled oxime (methyl 2-dimethylamino)-N-hydroxy-2-oxo-[1- ^{14}C] ethanimidothioate; a hydrolysis product and a principal metabolite of oxamyl): Batch No., E62727; specific activity, 116 $\mu\text{Ci}/\text{mg}$; adjusted for dosing: 100 mg/kg dose - 8120 dpm/ μg and 1 mg/kg dose - 71725 dpm/ μg ; radiochemical purity, approximately 98%.

Nonradiolabeled oxamyl: Batch No. D1410-222; purity 99.2%

Nonradiolabeled oxime: Batch No. A2213-10; purity 100%

Test animals: CD rats (Sprague-Dawley strain) were obtained from Charles River Laboratories, Inc., Portage, USA. The test animal body weights were approximately 200 gm.

Study design

A pilot study was conducted using 1 rat/sex, and the test animals received a single dose of 1- ^{14}C -oxamyl (1 mg/kg bw). The dosing solution was prepared 1 hr before administration. After dosing, the test animals were individually housed, the urine samples were collected during 0-6, 6-24, and every 24 hr (hour) intervals up to 168 hrs. Fecal samples were also collected every 24 hrs. up to 168 hrs. Expired air was collected for analysis of the presence of $^{14}\text{CO}_2$. At the

termination of the study, the test animals were sacrificed and the carcasses were retained for measurement of radioactivity.

For the main study, a group of 5 male and 5 female rats received a single oral dose of radiolabeled oxamyl (1 mg/kg). The test animals were housed individually, and urine samples and fecal samples were collected in similar schedules as those in the pilot study. At 168 hrs. after dosing, the test animals were sacrificed. A blood sample was taken from each animal. The following tissues were collected for analysis:

heart	lungs
liver	kidneys
spleen	gastro-intestinal tracts
brain	ovaries/testes
carcass	skin
muscle	fat
bone	

For a qualitative tissue distribution study on oxamyl, a male and a female rat received a single oral dose of radiolabeled oxamyl (1 mg/kg). After 168 hrs. of dosing, the test animals were sacrificed, and whole body autoradiography was carried out.

A study with ¹⁴C-oxime conducted on 10 males which received radiolabeled oxime at 100 mg/kg and 2 males which received 1 mg/kg. Urine samples were collected at intervals of 0-8, 8-24, and 24-48 hrs after dosing. Fecal samples were collected at 0-24 and 24-48 hrs. The test animals were sacrificed at 48 hrs after dosing.

The analytical methods employed in these studies for identifying metabolites and in quantifying the radioactivity were: thin layer chromatography (TLC), high performance liquid chromatography, mass spectrometry, liquid scintillation counting and enzymatic hydrolysis. The metabolites were identified by using a combination of the above analytical methods and synthetic reference compounds. The details of these analytical methods are excerpted from the report and presented in Appendix A.

A dated and signed statement for quality assurance and GLP compliance was included in the report.

Results

Pilot study: After 2 rats (1/sex) received a single oral dose of radiolabeled oxamyl (1 mg/kg), approximately 93% and 95% of the administered radioactivity was eliminated in urine by a male and a female rat within 168 hrs, respectively (Table 1).

Approximately 84% of dose was eliminated during the first 24 hrs after dosing. Less than 3% of the administered radioactivity was found in the feces, and that in the carcass was approximately 4%. Minimal amount of the radioactivity was found in the expired air (<0.6% of dose). A sex difference in the patterns of oxamyl elimination was not seen.

Main study: The results of the main study show similar patterns of elimination as those of the pilot study (Table 2). Approximately, 91% of the dose was eliminated for the duration of the study (168 hrs), and majority of this was eliminated during the first 24 hrs (80% of the dose). Approximately 2% and 1% of the dose were found in the feces and carcass, respectively. The total recovery was Approximately 95% of the dose.

Tissue distribution (quantitative): In general, oxamyl was not found to be sequestered in any tissue examined in excess of 2% of the dose after 168 hrs (7 days) of dosing (Table 3). Excluding the carcass and skin, the individual tissues examined contained less than 1% of the administered radioactivity, and the tissues which contained higher quantity of the radioactivity (as percent of dose) were skin, liver, muscle, whole blood, and G.I. tract. There was no sex difference in the amount of radioactivity in various tissues examined.

Whole body autoradiography: The reproduced copies of the autoradiograms were not clear and were difficult to interpret. However, a summary of the radioactivity in various tissues is presented in Table 4. The highest concentration of radioactivity was found in stomach and in the fur. The radioactivity found in the fur could well be a contamination of urinary radioactivity. In general, the whole body autoradiographic findings were consistent with those of the quantitative findings (Table 3).

Oxime study: After a single oral dose of radiolabeled oxime at a dose level of either 100 mg/kg or 1 mg/kg, greater than 90% of the administered dose was eliminated in the urine during the first 24 hrs after dosing (Table 5). Approximately 2.3 and 1.3% of the dose was eliminated in the feces of rats of 100 and 1 mg/kg rats, respectively. The results showed that the pattern of elimination for oxime and oxamyl were similar (See Tables 2 and 5), except that the radioactivity of oxime was eliminated faster than that of oxamyl during the first 24 hrs after dosing.

Analyses of the urinary metabolites: The urine samples (0-24 and 24-48 hrs) were pooled and analyzed for metabolites by thin layer chromatography (TLC) using different solvent systems. The main radioactive fraction was found to be a

polar base-line component and was eluted from the base-line in TLC system B (Figure 1). This fraction was referred to as Metabolite A, which accounted for approximately 37% and 31% of the dose in male and female rats (0-24 hrs), respectively (Table 6). The results of the mass spectrometry analysis indicated that Metabolite A was the β -glucuronide of the oxime.

Two radioactive components, E and F, were shown to be associated with the reference compounds, oxime and oxamyl, respectively (Figure 1 & Table 6). The association of Component E to oxime was also confirmed by mass spectrometry analysis. Component E or oxime accounted for approximately 13% of the dose in males and 18% in females while Component F or oxamyl was approximately 7% in males and 11% in females (Table 6).

Three other peaks, which were referred to as Metabolites B, C, and D, were also found (Figure 1 & Table 6). The results of mass spectrometry and chromatography indicated that Metabolite D was a compound which could readily degrade to 1-cyano-N,N-dimethyl formamide (DMCF). Metabolites B and C were not identified due to low concentrations in the pooled urine.

The TLC chromatograms of pooled urine samples of rats treated with 1 mg/kg oxamyl, 1 mg/kg oxime, or 100 mg/kg oxime were similar except for the expected absence of peak F (oxamyl) in oxime treated rats (Figure 2).

A representative sample of pooled urine from oxamyl or oxime treated rats was treated with the β -glucuronidase/sulfatase. The results showed that Metabolite A was partially hydrolyzed after treatment with the enzyme. With the enzyme treatment the radioactivity associated with oxime (Component E) was increased from 18% to 34% of the dose (Tables 7A & B). The radioactivity associated with D & F was slightly decreased whereas that associated with oxamyl was not changed.

Discussion

When 5 male and 5 female rats received a single oral dose of ^{14}C -oxamyl (1 mg/kg), approximately 80% of the administered radioactivity was eliminated in the urine by 24 hrs after dosing, and approximately 91% of the dose was eliminated in the urine by 168 hrs. Less than 3% of the dose was found in the feces, and approximately 1% of the dose was found in the carcass. Less than 1% of the dose was found in any tissue examined. The data indicated that oxamyl was readily absorbed with oral administration and rapidly metabolized and eliminated in the urine. There was no sex difference in the patterns of elimination, and essentially no sequestration of

oxamyl or its metabolites was seen in any tissue examined.

With chromatographic analysis, several peaks, which corresponded to different metabolites, were found. To avoid the acute toxicity of oxamyl and for the purpose of characterizing the metabolites, a principal hydrolysis product of oxamyl, oxime, was administered to rats at a much higher dose (100 mg/kg). The elimination patterns of oxamyl and oxime were similar. The major metabolite of oxamyl was identified to be β -glucuronide of the oxime (Metabolite A). Based upon these findings a metabolic pathway was proposed (Figure 3). In this scheme, the major route of metabolism was that hydrolysis of oxamyl to oxime which was then conjugated with glucuronide.

OXAMYL

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