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12-1-89

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

DEC-1 1989

006944

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Oxamyl: Evaluation of a 21-day dermal toxicity study
Caswell No. 561A Accession No. 408276
Record No. 232128 Tox. Project No. 8-1279

TO: D. Ewards, PM(12)
Registration Division (767c)

FROM: Whang Phang, Ph.D. 11/23/88
Pharmacologist
Tox. Branch / HFAS / HED (769c)

THROUGH: James N. Rowe, Ph.D. James N. Rowe 11/23/88
Acting Section Head
and
Marcia van Gemert, Ph.D. 11/29/88
Acting Branch Chief
Tox. Branch / HFAS / HED (769c)

In response to the requirements stated in the Registration Standard of Oxamyl, E.I. du Pont de Nemours & Co., Inc. submitted a 21-day dermal toxicity study in rats. The study has been reviewed, and the conclusion is as follows:

Groups of rabbits were dermally applied 2.5, 50, and 250 mg/kg of IN D1410-196 for 6 hrs/day for 22 consecutive days; both males and females of 50 and 250 mg/kg groups showed significant decrease in plasma, in red blood cell, and in brain cholinesterase activity. In addition, there was an increase in serum glucose level in both 250 mg/kg males and females. There were other sporadic changes in clinical chemistry, but they were not considered to be compound-related effects. Based upon these findings, the NOEL was 2.5 mg/kg; LEL, 50 mg/kg.

This study is classified as supplementary because the report does not have any data on chemical analysis of the test article. It could be upgraded to minimum when adequate data on the chemical analysis are submitted.

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Reviewer: Whang Phang, Ph.D. 11/23/88
Section II, Tox. Branch / HFAS (769c)
Secondary Reviewer: James N. Rowe, Ph.D. James N. Rowe 11/23/88
Section II, Tox. Branch / HFAS (769c)

DATA EVALUATION REPORT

STUDY TYPE: 21-day dermal toxicity-rabbit

CHEMICAL: Oxamyl; IN D1410-196; Ethanimidothioic acid, 2-(dimethylamino)-N-[[(methylamino)carbonyl]oxy]-2-oxo-, methyl ester

TOX. CHEM. NO.: 561A Accession #: 408276

RECORD NO.: 232128 TOX. PROJECT NO.: 8-1279

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

PERFORMING LABORATORY: E.I. du Pont de Nemours & Co., Inc.
Haskell Laboratory for Toxicology and Industrial Medicine
Newark, Del. 19714

CITATION: Brock, W. J. (1988). Repeated dose dermal toxicity: 21-day study with IN D1410-196 in rabbits. Haskell Laboboratory for Toxicology and Medicine. HL Report No. 523-88. Sept. 19, 1988.

CONCLUSION:

Groups of rabbits were dermally applied 2.5, 50, and 250 mg/kg of IN D1410-196 for 6 hrs/day for 22 consecutive days; both males and females of 50 and 250 mg/kg groups showed significant decrease in plasma, in red blood cell, and in brain cholinesterase activity. In addition, there was an increase in serum glucose level in both 250 mg/kg males and females. There were other sporadic changes in clinical chemistry, but they were not considered to be compound-related effects. Based upon these findings, the NOEL was 2.5 mg/kg; LEL, 50 mg/kg.

This study is classified as supplementary because the report does not have any data on chemical analysis of the test article. It could be upgraded to minimum when adequate data on the chemical analysis are submitted.

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A. MATERIAL:

Test compound: Oxamyl (toxicology sample); 97.2% pure; white crystal. The chemical analysis of the test compound was not included in the report.

Test animals: Approximately 8 weeks old New Zealand White rabbits which weighed 1625-1971 gm were obtained from Hare Marland, Hewitt, NJ.

B. STUDY DESIGN:

A dose-range finding study was conducted to determine the irritation potential of Oxamyl or IN D1410-196, the effects of the test compound on blood and brain cholinesterase activity, and the appropriate doses to be used in the main study. Therefore, 2 rabbits/dose were treated topically with 100, 500, 750, & 1000 mg/kg of the test article for 6 hours (hr)/day for 5 days. In addition, rabbits were treated topically with doses of 5 or 25 mg/kg of test article for similar periods of time to determine at what dose levels would cholinesterase activity be affected. Furthermore, one rabbit was treated topically once for 6 hrs with 500 mg/kg of the test compound for determining the blood and brain cholinesterase activity. The results are presented in Table 1. An effect on the cholinesterase activity was seen at a dose as low as 25 mg/kg of Oxamyl. No dermal irritation was observed in any treated animals. Based upon these findings, doses of 2.5, 50, and 250 mg/kg were selected for the 21-day dermal toxicity study.

For the main study, the hair of scapular to lumbar region of the back of each rabbit was shaved, and the rabbits were fitted with plastic collars to prevent ingestion of the test material. The rabbits were randomly assigned into four groups. The two lower dose groups (2.5 and 50 mg/kg) consisted 5 animals/sex/dose; control and high dose groups, 10/sex/dose.

The test article was mixed with distilled water to form a paste which was applied onto the shaved skin of the test animals at doses of 2.5, 50, and 250 mg/kg for 6 hrs/day for 22 consecutive days. The amount of material applied was adjusted daily according to the current weight. After the material was placed on the treated site, the site was covered with sterile gauze pads. The rabbits were then wrapped with layers of plastic film. Groups of controls were treated with distilled water in a similar fashion as the treated animals.

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After 6 hrs of treatment, the test article was removed from the application site by washing with warm water. The rabbits were observed for dermal irritation and clinical signs of toxicity daily. After 21 days of treatment, the surviving controls and 250 mg/kg rabbits were observed for a 14-day period (recovery period) for any clinical signs. Dermal irritation was evaluated according to the Draize scale (Table 2).

The animals were weighed twice weekly prior to or during the treatment period and once weekly during the recovery period. Food consumption was determined weekly. Mean food consumption and food efficiency were calculated.

Blood samples were collected from each rabbit 9 days prior to the first treatment and approximately 1 hr following the last treatment. In addition, blood samples were collected from the animals in the recovery groups on test day 36. The following hematological parameters were examined:

erythrocyte	leukocyte
differential leukocyte	platelet counts
hemoglobin	mean corpuscular hemoglobin
hematocrit	mean corpuscular hemoglobin concentration
mean corpusculr hemoglobin volume	

The following clinical chemistry parameters were examined:

alkaline phosphatase	alanine aminotransferase
aspartate aminotranferase	blood urea nitrogen
serum protein	albumin
globulin	creatinine
cholesterol	bilirubin
glucose	calcium
sodium	potassium
chloride	phosphorus
plasma cholinesterase	blood cholinesterase
red blood cell cholinesterase	brain cholinesterase

Pathology evaluation:

On day 22 of the study, 5 males and 5 females of the controls, 4 males and 5 females of the high dose, and all animals in low and mid dose groups were sacrificed. The following tissues were collected for microscopic examination:

brain*	adrenal*	liver*
spleen*	kidney*	testes*
thymus	bone, bone marrow	heart
lymph nodes	aorta	trachea

lungs	salivary glands	esophagus
stomach	small intestine	large intestine
gallbladder	pancreas	urinary bladder
pituitary	thyroid	parathyriod
prostate	epididymides	ovaries
corpus & cervix uteri	vagina	spinal cord
sciatic nerve	eye	skeletal muscle
treated & untreated skin		all gross lesions

* these tissues were weighed, and their relative weights were calculated.

Statistical Analyses: The following statistical analyses were used:
One-way analysis of variance
Least significant difference test
Fisher's Exact test
Bartlett's test
Dunnett's test
Kruskal-Wallis and Mann-Whitney U tests

RESULTS

Body weight: Mean body weights of treated rabbits were comparable to those of the controls (Table 3). The body weight gains of treated animals did not show any meaningful difference from those of the control animals.

Food consumption and food efficiency: No significant difference was observed in food consumption and in food efficiency between treated and control animals (Table 4).

Clinical observations & mortality: An increase in the incidence of epidermal scaling was seen in 250 mg/kg females relative to the controls (Table 5).

Three male rabbits in the high group died during the test, but the cause of death "could not be determined", but it was not considered to be related to cholinesterase inhibition.

Clinical Laboratory Results:
Hematology: The results of the hematology parameters indicate no compound-related effects were seen in treated animals.

Clinical chemistry: Cholinesterase activities in plasma, in red blood cell, and in the brain were all decreased in 50 and 250 mg/kg rabbits at day 22 of the test, and the decrease was statis-

tically significant (Table 6A & B). There was an increase in glucose level of high dose males and females, and this increase was significantly different from the controls (Table 7). There were other sporadic changes, but they were not considered to be compound-related.

Pathology evaluations:

Organ weights and the ratios of organ weight/body weight were comparable between treated and control animals (Table 8A & B).

Histopathology results indicated that an increase in the incidence of an accumulation of eosinophilic material within the interglandular stroma of Brunner's glands of the duodenum of the high male and female rabbits (control: 0/5; High dose males: 2/7; high dose females: 3/4). According to the report, morphologically this material resembled amyloid, but Congo stain was negative. This microscopic finding was not observed at the recovery sacrifice, and the toxicological significance of this finding could not be determined.

DISCUSSION:

When groups of rabbits were dermally applied 2.5, 50, and 250 mg/kg of IN D1410-196 for 6 hrs/day for 22 consecutive days, both males and females of 50 and 250 mg/kg groups showed significant decrease in plasma, in red blood cell, and in brain cholinesterase activity. In addition, there was an increase in serum glucose level in both 250 mg/kg males and females. There were other sporadic changes in clinical chemistry, but they were not considered to be compound-related effects. Based upon these findings, the NOEL was 2.5 mg/kg; LEL, 50 mg/kg.

Although the report does not include individual animal data of food consumption, the body weight data do not indicate any change in the body weights of treated animals relative to those of the controls. Therefore, the absence of the individual animal food consumption data dose not present much difficulty in interpreting the results. However, the registrant should submit the data on chemical analysis of the test article. This study is classified as supplementary. It can be upgraded to minimum when adequate chemical analysis data are submitted.

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OXAMYL

Page _____ is not included in this copy.

Pages 7 through 16 are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

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