CASWELL FILE

Reviewed by: Whang ang, Ph.D. 7/26/88
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Section III, Toxicology Branch (TS-769c)

DATA EVALUATION REPORT

STUDY TYPE: Mutagenicity: In vitro unscheduled DNA synthesis (UDS) assay in rat primary hepatocytes

CHEMICAL: Oxamyl; IND 1410

EPA ACCESSION NO.: 406065-08 CASWELL NO.: 561A

EPA RECORD NO.: 222981/222982 EPA PROJECT NO.: 8-0881

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

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

CITATION: Vincent, D.R. (1982). Assessment of IND 1410-196 in the in vitro unscheduled DNA synthesis assay in rat hepatocytes. Haskell Laboratory; Report No.: 719-82. Nov 18, 1982. Submitted by E. I. du Pont de Nemours & Co., Inc.; April 29, 1988.

SUMMARY: Under the testing conditions, the results appear to indicate that IND 1410-196 was negative in UDS assays with rat primary hepatocytes, but the report has not presented data on silver grain counts in individual cells. Lack of individual data prevents verification of the results presented in the report. Therefore, the study is classified as Unacceptable.

METHODS AND MATERIALS:

Test Compound: IND1410-196; Oxamyl (toxicological sample which is different from the technical) 97.1% purity.

Cells: Hepatocytes were primary cells isolated from male Sprague-Dawley rats.

Postive control agents: 7,12-dimethylbenz[a]anthracene (DMBA)

Solvent for test agent: PBS (phosphate buffered saline)

EXPERIMENTAL PROCEDURES:

The details of the experimental protocol are excerpted from the submitted report (Haskell Lab. Report No.: 719-82) and presented in the Appendix. In summary, isolated hepatocytes were cultured on plastic coverslips, and the primary cell cultures were incubated

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with 5 uCi/ml [methyl-^{3}H]-thymidine and the test agent at concentrations of $1x10^{-5}$ to 10 mM for 18 hours. After treatment the nuclei of the cells were swelled with 1% sodium citrate and fixed with ethanol-glacial acetic acid (3:1). The cells were prepared for autoradiographic analysis; subsequently, quantitation of UDS was conducted by counting the silver grains in the developed emulsion layer over the nuclei. Duplicate treatments were conducted for each dose level.

RESULTS:

Viabilities of stock hepatocytes were reported to be 84% and 70% in trial 1 and trial 2, respectively. Cytotoxicity was reported to be determined by fewer than 25 hepatocytes available for scoring per slide. In trial 1 cytotoxicity was not seen. In trial 2 cytotoxicity was found in 5.0 and 10.0 mM assays where very few nuclei were found for analysis (Tables 1 & 2).

For UDS assays, a test compound was considered positive when the average net nuclear grain count was at least five in two trials. The IND 1410-196 treated cells at any concentration showed negative average net silver grains per nucleus; in comparison, the positive control showed significant increase in net nuclear grain count (Tables 1 & 2).

DISCUSSION AND CONCLUSION:

Although under the testing conditons, the results appear to indicate that IND 1410-196 was negative in UDS assays with rat primary hepatocytes, the report has not presented data on silver grain count in individual cells. Lack of individual data prevents verification of the results presented in the report. Therefore, the study is classified as Unacceptable.

There is a question concerning the test article, IND 1410-196. The registrant informed the Agency during a meeting held on July 12, 1988 that IND 1410-196 is synthesized in the laboratory for toxicological testing, and it does not contain three contaminants as does the technical grade. The registrant has been requested by the Agency to provide a logical explanation for this difference.

OXAMYL

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Reviewed by: Whang ang, Ph.D. 7/26/88
Secondary Reviewers: Marcia van Gemert, Ph.D. 7/26/88
Section III, Toxicology Branch (TS-769c)

DATA EVALUATION REPORT

STUDY TYPE: Acute dermal toxicity study-rabbits

EPA ACCESSION NO.: 406065-01 CASWELL NO.: 561A

EPA RECORD NO.: 222981/222982 EPA PROJECT NO.: 8-0881

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

TESTING LABORATORY: Haskell Laboratory for Toxicology and Indus-
Medicine, E. I. du Pont de Nemours & Co., Inc.

CITATION: Brock, W. J. (1988). Acute dermal toxicity study of IND 1410-196 rabbits. Haskell Laboratory; Report No.: 114-88. March 2, 1988. Submitted by E. I. du Pont de Nemours & Co., Inc.; April 29, 1988.

METHODS AND MATERIALS:

Test Compound: IND1410-196; Oxamyl (toxicological sample which is different from the technical) 97.1% purity. White crystalline solid.

Test Animal: New Zealand White rabbits weighing between 1972 and 2691 gm were obtained from Hare Marla nd, NJ. Age of the test animals was not reported.

Experimental Procedures: The protocol of the study is excerpted from the submitted report (Haskell Laboratory Report No.: 114-88) and presented in the Appendix. Briefly, the test article as a paste was applied to shaved area of the rabbits (5/sex/dose) at doses of 2000, 3500, and 5000 mg/kg for 24 hrs. After 24 hrs the treated area was washed, and the animals were observed for 14 days.

RESULTS:

Mortality: In treated males, 2/5 rabbits of 3500 and 5000 mg/kg groups, died on days 3 and 2, respectively (Table 1). In female rabbits, 1/5 of 2000 and 3500 groups died.

Dermal Irritation: It was reported that in treated animals no to mild erythema and edema were observed in the rabbits by 24 hours after treatment. The dermal irritation had essentially resolved by day 5 in most animals. No dermal irritation was evidenced at the end of the study (day 14).

TABLE 1†

Mortality Rates of IND 1410-196 Dermally Treated Rabbits

Dose (mg/kg)	Mortality
Males	
2000	0/5
3500	2/5
5000	2/5
Females	
2000	1/5
3500	1/5
5000	0/5

† Data excerpted from the submitted report.

Clinical signs: The report stated that no clinical signs of toxicity were observed in any of the treated rabbits.

Body weights: Initially, there appeared to be a slight drop in body weight in most treated males and females, but the weight loss was recovered by day 7.

Gross pathology: Based upon the individual animal data, most rabbits, which died during the study, were under going mild autolysis. Gross observations of some of these animals were consistent with cholinesterase inhibition.

DISCUSSION AND CONCLUSION:

Based upon the experimental results of this study, the LD_{50} of acute dermal toxicity for male rabbits was greater than 5000 mg/kg, and that for female rabbit could not be calculated from the data which yielded a negative slope. However, under the present circumstances the LD_{50} for female rabbit was considered to be greater than 2000 mg/kg.

The results of this study are in sharp contrast to those of the acute oral toxicity study. In acute oral toxicity study, the LD_{50} was found to 3.1 mg/kg for male rats and 2.5 mg/kg for female rats. Although this comparison involved different species of animals, it indicated that in acute dermal toxicity study much of the applied IND 1410-196 was not absorbed through the skin.

Although the study has minor deficiencies, the results of the study provide useful information. In addition the deficiencies do not affect the interpretation of the study. However, there is a question concerning the test article, IND 1410-196. The registrant has informed the Agency during a meeting held on July 12, 1988 that IND 1410-196 is synthesized in the laboratory for toxicological testing, and it does not contain three contaminants as does the technical. The registrant has been requested by the Agency to provide a logical explanation for this difference. Under the present circumstances, this study is classified as Supplementary. After receipt and satisfactory evaluation of the explanation concerning the test article, this study may be upgraded.

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