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005031

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DATA EVALUATION RECORD

ASSURE (NC-302)

Repeated Dose/21-Day Dermal Toxicity Study in Rabbits

STUDY IDENTIFICATION: Loveless, S. E. Subacute dermal toxicity study (21 days) of INY-6202-15 (NC-302 technical) in rabbits. (Unpublished study No. 411-83 prepared by Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE, and submitted by E. I. duPont de Nemours and Co., Inc., Wilmington, DE; dated October 11, 1983.) Accession No. 073530.

APPROVED BY:

I. Cecil Felkner, Ph.D.
Department Manager
Dynamac Corporation

Signature: I. Cecil Felkner

Date: 4-8-86

1. CHEMICAL: Assure; INY-6202-15; NC-302; propanoic acid, 2-[4-(6-chloro-2-quinoxalin-2- yloxy)-phenoxy]-, ethyl ester; ethyl 2-[4-(6-chloro-2-quinoxalinyloxy)phenoxy]propionate.

2. TEST MATERIAL: INY-6202-15 (NC-302 technical), lot No. 8002, contained 99.1% active ingredient and was described as a white crystal.

3. STUDY/ACTION TYPE: Repeated dose/21-day dermal toxicity study in rabbits.

4. STUDY IDENTIFICATION: Loveless, S. E. Subacute dermal toxicity study (21 days) of INY-6202-15 (NC-302 technical) in rabbits. (Unpublished study No. 411-83 prepared by Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE, and submitted by E. I. duPont de Nemours and Co., Inc., Wilmington, DE; dated October 11, 1983.) Accession No. 073530.

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7. CONCLUSIONS:

A. Repeated dermal application of 0, 125, 500, and 2000 mg/kg of INY-6202-15 to shaved skin of New Zealand white rabbits produced clinical signs that were sporadic and not compound related. There was no mortality at any dose level. No compound-related effects were detected in either hematologic, clinical chemistry, or histopathologic studies immediately following 21 days of dosing or the 15-day recovery period. In this study the NOEL is 2000 mg/kg.

B. Core Classification: Supplementary.

8. RECOMMENDATIONS: Organ weights were taken at necropsy; however, no values were reported. All data should be reported. Specific skin irritation observations and food consumption measurements were not taken. These parameters are generally required for subacute dermal studies.

Items 9 and 10--see footnote 1.

11. MATERIALS AND METHODS (PROTOCOLS):

A. Materials and Methods:

The 40 New Zealand white rabbits used for study were received from Dutchland Labs, Inc., Denver, PA, and the body weights ranged from 1.9-2.3 kg for males and 1.8-2.3 kg for females. The animals were acclimated to laboratory conditions for 2 weeks before the start of the study; food and water were available ad libitum.

The test material was applied dermally as an aqueous paste to groups of five male and five female rabbits at dose levels of 0, 125, 500, and 2000 mg/kg. A stock paste was prepared daily.

The dorsal trunk area of the rabbits was clipped free of hair. They were then fitted with plastic collars. Freshly prepared test material doses were adjusted according to daily body weights, applied to the clipped area of the intact back skin, and covered with gauze pads. The trunk of each rabbit was then wrapped with a layer of plastic wrap, stretch gauze bandage, and elastic adhesive tape. Six hours later, the gauze pads and wrapping were removed and the test site was rinsed with tepid water and patted dry. This procedure was repeated daily for 21 consecutive days. The control rabbits were treated with water using the identical procedure.

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[1] Only items appropriate to this DER have been included.

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All animals were observed daily for mortality and toxic effects. Body weights were taken twice prior to the start of dosing, once daily during the dosing period, and once weekly during the recovery period. Hematologic and clinical chemistry analyses were performed on all animals 3 days prior to the start of dosing, 1 day after the last dose, and 15 days after the last dose for the remaining recovery rabbits.

Six rabbits from each dose group were sacrificed 1 day after the last application, and the remaining animals were sacrificed 15 days later. A complete necropsy was performed on all animals. The following organs were weighed at necropsy: liver with gall-bladder, kidneys, spleen, thymus, and testes-epididymides. Organs and tissues from each animal were preserved in a suitable fixative (fixative not identified).

Histologic sections were made of all harvested organs and gross lesions for microscopic evaluation.

B. Protocol: See Appendix A.

12. REPORTED RESULTS:

A. Clinical Observations and Mortality: There were no deaths in either the controls or the dose groups. The clinical signs observed in the rabbits were as follows:

Sex	No. of Rabbits	Dose (mg/kg/day)	No. of Days	Clinical Signs
M	5	Control	21	None.
F	5	Control	21	Occasional diarrhea; pustules on the back of one rabbit for 5 days.
M	5	125	21	Occasional diarrhea; pustules on the back of one rabbit for 2 days.
F	5	125	21	Occasional diarrhea.
M	5	500	21	Pustules on the back of one rabbit for 1 day.
F	5	500	21	Occasional diarrhea.
M	5	2000	21	None.
F	5	2000	21	None.

B. Body Weights: During the first 10 days, body weights fluctuated in all groups but were similar to predose weights. During the remainder of the study, the body weight gains were consistent. There were no significant differences in body weight in either sex or dose when compared to controls.

C. Hematology: One day after the last test material application the 500-mg/kg males showed a significant ($p \leq 0.05$) increase in the leukocyte count when compared to controls. There were no other compound-related changes at 1 day and 15 days after the last dose. Three days prior to the start of dosing the 125-mg/kg female group showed a significant ($p \leq 0.05$) increase in neutrophil count when compared to control.

D. Biochemistry: There were no changes in biochemical parameters that were related to dosing. One day after the last dose in males, serum alkaline phosphatase was significantly ($p \leq 0.05$) higher in the 125-mg/kg group when compared to controls. At all male dose levels, the serum sodium level was significantly ($p \leq 0.05$) higher than controls 15 days after the last dose. No further significant differences were observed in the females at either 1 day or 15 days after dosing.

E. Necropsy: No compound-related effects were observed following sacrifice at 1 day and 15 days after the last dose in animals of either sex.

F. Microscopic Pathology: The microscopic findings observed in this study were reported as incidental or spontaneous changes or the result of intercurrent disease. None were related to the administration of the test compound.

13. STUDY AUTHOR'S CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. Systemic effects observed in animals among all dose groups and the controls included sporadic weight loss, diarrhea, and small pustules. These signs were not compound related. Hematologic and biochemical analyses and histopathologic evaluation revealed no compound-related effects immediately following 21 days of dosing or after a 15-day recovery period. In conclusion, INY-6202-15 at doses up to and including 2000 mg/kg did not cause toxicity following 21 days of dermal exposure.

B There was no quality assurance statement included with this study.

14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

The test material appeared to have no significant effect on the body weights of the study animals. The fluctuations in body weight during the first 10 days could be attributed to fluctuations in food consumption due to the stress of handling and the mechanics of test material

application. Organ weights were taken at necropsy following 21 days of exposure and 15 days of recovery, but there were no organ-body weight data presented. We agree with the study author that doses up to 2000 mg/kg did not produce any compound-related systemic toxicity after 21 days of exposure. The NOEL for this study is 2000 mg/kg.

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Item 15--see footnote 1.

16. CBI APPENDIX: Appendix A, Protocol, CBI pp. 2-11.

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APPENDIX A

Protocol

APPENDIX A

Protocol

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Page_____ is not included in this copy.

Pages 9 through 18 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

____ 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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X FIFRA registration data.

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