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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Review of a Rat Metabolism Studies with Rotenone (Reg. No. 6704-Q). EPA Acc. No. 258849. Tox. Chem. No. 725.

TO: William Miller
Product Manager (16)
Registration Division (TS-767C)

THRU: Jane Harris, Ph. D., Section Head JH 9/6/85
Review Section 6
Toxicology Branch
Hazard Evaluation Division (TS-769)

FROM: Roger Gardner, Toxicologist
Review Section 6 Roger Gardner 9-4-85
Toxicology Branch
Hazard Evaluation Division (TS-769)

Actions Requested

Review of a series of rat metabolism experiments.

Recommendations and Conclusions

1. The report is a finalized version of one submitted in draft form by the U. S. Fish and Wildlife Service (FWS) under Accession Number 253333. There were no substantial changes in the most recent report (see Sections I., II., and III, below).

2. Rotenone is primarily excreted in the feces after oral and intravenous doses (95 to 97% of the radioactivity recovered during the 144 hours following dosing and approximately 75% recovered within 48 to 72 hours). The route of administration, dose level, and number of doses had no apparent effect on the excretion pattern (see Section II). Enterohepatic circulation may also occur during excretion.

3. The Core Classification for the metabolism studies is "Acceptable" and that for the acute oral experiment is "Minimum."

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I. Background

Rotenone is a plant root extract (derris or cube roots) which is used as an insecticide or piscicide. Its chemical name is [2R-(2a, 6a, 12a)]-1, 2, 12, 12a-tetrahydro-8, 9-dimethoxy-2-(1-methylethenyl)[1]benzopyrano-(3, 4-yl-furo(2, 3-dibenzopyran-6, (6aH)-one. The principal active ingredient is associated with derris or cube resins (depending upon the source of the rotenone extract) which are also classified as active ingredients. Formulations contain rotenone and associated resins in a ratio of 1:2 (see Environmental Protection Agency unpublished report dated May, 1980. Rotenone: PreRPAR Review. Office of Pesticides and Toxic Substances.). Rotenone can be separated from the resins to a purity of 99.5%.

II. Summary of Metabolism Results

Results of the submitted report generally characterized the excretion pattern associated with single or repeated (14 consecutive days) low doses (0.01 mg/kg) and a single high dose (5 mg/kg) oral doses as well as a single low intravenous dose (0.01 mg/kg). The major route of excretion (95 to 97% of the administered dose) is in the feces, and female rats excrete administered radioactivity at a slower rate than males (75% of the dose was accounted for in the feces 72 hours after dosing for females and 48 hours after dosing in males). The route of administration, dose level, and number of doses had no apparent effect on the excretion pattern.

There is a sex difference with respect to the acute oral toxicity of rotenone in that female rats are more sensitive than males. The calculated oral LD_{50} for females is approximately 40 mg/kg, while that for males is approximately 100 mg/kg. Based on these results, the purified rotenone (95+%) used in the metabolism study should be classified into Toxicity Category I.

III. Discussion

Radiolabeled residues in plasma samples from rats given the low oral doses could not be detected, and radioactivity was unextractable from feces of those rats . In addition, results from tissue analyses from rats given the 5 mg/kg dose contained relatively low concentrations (<0.5 ppm) at 96 to 144 hours after dosing. These results are consistent with the rapid distribution and excretion indicated by the pharmacokinetics experiments. Based on these considerations tissue analyses for animals sacrificed at 12 and 24 hours following dosing is more appropriate for characterization of absorption and distribution after dosing.

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Variability in tissue and plasma results is expected at such low residue concentrations as those observed in the rotenone experiments (<1 ppm). That variability and the generally accepted practice of using 3 to 6 animals in each experiment are limitations considered in the selection of statistical analyses for results from metabolism studies like that submitted by the FWS. Techniques such as pooling of data from both sexes before weighted nonlinear regression analysis (a technique used in the pharmacokinetics experiment) may not be appropriate in view of the sex differences suggested by results from the acute toxicity studies. In the enterohepatic circulation experiment, use of the exact permutations test is more appropriate for larger sample sizes, especially when the data vary as much as the results reported in the rotenone study and the samples are considered to be random.

A more detailed review of the submitted report can be found in a previous Toxicology Branch review dated September, 1985 (see memorandum from R. Gardner to W. Miller, Registration Division. Subject: Review of a Draft Final Report on Rat Metabolism Studies with Rotenone and Request for Comments. (Reg. No. 6704-Q) Tox. Chem. No. 725.).