EPA Reviewer: SanYvette Williams, D.V.M. Signature:
Review Section IV, Toxicology Branch II, Date: 8-11-92
Health Effects Division

EPA Section Head: Elizabeth Doyle, Ph.D. Signature:
Review Section IV, Toxicology Branch II, Date: 8/13/92
Health Effects Division

DATA EVALUATION REPORT

STUDY TYPE: Metabolism in Rats

EPA IDENTIFICATION NUMBERS:

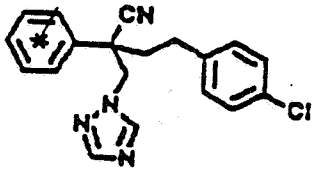
Tox. Chem. Number: 723-Q

HED Number: 1-2499

MRID Number: 418750-17; 418750-18

TEST MATERIAL: RH-7592 (CASRN 114369-43-6)

SYNONYM: [2-(4-Chlorophenyl)ethyl]-phenyl-~~1~~-1H-1,2,4-triazole-1-propanenitrile



The [^{14}C]-label (*) was uniformly distributed in the unsubstituted phenyl ring.

SPONSOR: Rohm and Haas Company, Toxicology Department, 727 Norristown Road, Spring House, PA 19477

TESTING FACILITY: Hazleton Laboratories America, Inc., 3301 Kinsman Boulevard, Madison, WI 53704 (Report 1). Rohm and Haas Co., 727 Norristown Rd., Spring House, PA 19477 (Report 2).

AUTHORS: Leon LeVan (Report 1) and Richard Hanauer (Report 2)

REPORTS: 1. ^{14}C-RH-7592: Pharmacokinetic Study in Rats. Rohm and Haas Report No. 88RC-0071. 221 pp. Lab Project ID No.: HLA 6228-102.

2. ^{14}C-RH-7592: Range-Finding Kinetic and Metabolite Identification Study in Rats. Rohm and Haas Report No. 34-90-74. 327 pp.

DATE: August 3, 1990 (Report 1) and March 8, 1991 (Report 2)

CONCLUSIONS: The absorption, distribution, metabolism, and excretion of RH-7592 were studied in groups of male and female Sprague-Dawley rats administered a single oral gavage dose of 1 or 100 mg/kg [^{14}C]RH-7592, or 1 mg/kg unlabeled RH-7592 in the diet for 14 days followed by a single gavage dose of 1 mg/kg [^{14}C]RH-7592 on day 15. An additional group of rats were administered a single intravenous injection of 1 mg/kg [^{14}C]RH-7592.

[^{14}C]RH-7592 was rapidly absorbed, distributed, metabolized, and excreted in rats for all dosing regimens. The 4-day recoveries were at least 82.6% of the administered dose for all dosing groups. The elimination of radioactivity in the feces (75.6-83.7% of administered dose) and urine (5.46-12.60%) were almost comparable for all oral-dose groups, with slightly higher radioactivity in the feces of the repeated oral-dosed group than the single-dose groups. The radioactivity in the blood peaked at 3 hours for the low-dose group and 3-6 hours in the high-dose group, indicating biphasic elimination. In the intravenous group, most of the recovery was in the feces (77.2-91.40% of administered dose). Therefore, the elimination and pharmacokinetic data suggest that absorption of RH-7592 is rapid, bioaccumulation is low, and excretion is primarily in the feces due to biliary excretion. The study also indicates that RH-7592 and/or its metabolites do not bioaccumulate to an appreciable extent following oral or intravenous exposure since all the tissues contained negligible levels (<1%) of radioactivity at 4 days postexposure.

The metabolism of RH-7592 appears to be extensive because the unmetabolized parent compound represented a minor amount of the recovered radioactivity in the excreta. Thirteen metabolites of RH-7592 and their conjugates were identified in the high-dose group. The highest radioactivities in the urine was represented by ketoacid, 3- and 4-phenol conjugates, and sulfate metabolites at 7 days postexposure. Lactone A and sulfates represented the highest radioactivities in the fecal extract. Sex-related differences were found for ketoacid and sulfate metabolites in the urine and feces. However, approximately 50% and 20% of the total radioactivity in the feces and urine, respectively, were not identified in the study, suggesting the lack of sensitivity of the analytical method used for metabolite analyses. Furthermore, dose-related differences of metabolism could not be determined since the metabolite pattern for the low-dose oral groups was not evaluated.

Based on these study results, oral absorption and fecal elimination of RH-7592 were not sex or dose related. There was a sex-related difference in the metabolism of a single oral dose of 100-mg/kg [^{14}C]RH-7592 in rats. A dose-related effect for metabolic pathway could not be determined. The study also showed that administration of 1 and 100 mg/kg RH-7592 did not induce any apparent treatment-related clinical effects.

STUDY CLASSIFICATION: The study is classified as Supplementary. This study may be upgraded if additional data are provided regarding metabolite analysis for the low-dose oral groups. Thus, a dose-related difference in metabolism could be evaluated. There were no other major deficiencies in this study that would affect the overall study results and conclusions.