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DATA EVALUATION REPORT

STUDY TYPE: Metabolism Study (rat): Tissue Distribution with Repeated Dosing

MRID NO.: 116493 TOX. CHEM. No.: 320

SPONSOR: The Boots Company Ltd., Nottingham (Phenoxyacid Herbicide Consortium)

TESTING FACILITY: Report prepared by Hazleton Laboratories Europe Ltd., England

CITATION: Gilbert, C.; Hopkins, R.; Bibby, M.; et al. (1978) The Metabolic Fate of (^{14}C)-dichlorprop (dl-2-(2,4-dichloro (Ring-u-14C) Phenoxy)propionic Acid) in the Rat: Report No. 1313R2-277/1. (Unpublished study received Mar 28, 1979 under 264-222; prepared by Hazleton Laboratories Europe Ltd., Eng., submitted by Union Carbide Agricultural Products Co., Inc., Research Triangle Park, NC; CDL:237982-A)

CONCLUSION:

Groups of rats (10/sex) were repeatedly administered radiolabelled and unlabelled 2,4-DP acid at a dose of 1 mg/kg/day for 14 days Groups of 2 rats/sex were sacrificed at 5 different dosing intervals. The tissue distribution of radioactivity was measured. The results indicated that only fat retained a small amount of radioactivity relative to all other tissues after 96 hr of dosing.

This study should include the examinations of excretion and metabolism of 2,4-DP acid with repeated dosing. It is classified as an unacceptable study.

MATERIALS:

a) Male and female Sprague Dawley rats were obtained from Charles River (UK) Ltd., Kent, England. They weighed between 140 and 250 gm.

b) Ring labelled ^{14}C-2,4-DP was used in the studies. The chemical analysis data indicated that specific activity was 4.7 mCi/mmol (20 uCi/mg), and radiochemical purity was 97%.

c) Unlabelled 2,4-DP was a white crystalline powder, and the chemical purity was assessed to be 99.7%.

METHODS:

Test Agent: 50 mg of ^{14}C-2,4-DP acid was ground in 250 ml of saline containing methyl cellulose (1%, w/v). The specific radioactivity of the suspension was determined before and after dosing; the mean specific radioactivity of the suspension used in this study was 4.27 uCi/ml or 21.4 uCi/mg.

Tissue Distribution: Groups of rats (10/sex) weighing 180-240 gm were administered by gavage radioactive 2,4-DP acid at a dose level of 1 mg/kg body in a volume of 1 ml/200 gm body weight (4.27 uCi/200 gm body weight) for 14 days. Two males and 2 females were sacrificed 24 hr after 1st, 5th, 10th, and 14th dose and also at 96 hr after the 14th dose. The concentration of radioactivity in plasma, fat, liver, skeletal muscle, adrenals, and thyroids was measured.

RESULTS:

The values of the mean tissue distribution of radioactivities in repeated-dose treated rats are shown in Table 1. No appreciable concentration of radioactivity was accumulated in any particular tissue. In both males and females fat showed a slight and gradual increase in radioactivity during the dosing period (14 days). In general, the concentration of radioactivity was lower in females than in males, and in both sexes the kidney contained higher concentrations of radioactivity at all times relative to those of the liver (Table 1). The mean concentrations of radioactivity in plasma were also high compared to other tissues.

DISCUSSION:

When rats were repeatedly dosed with 1 mg/kg of labelled and unlabelled 2,4-DP acid, no marked accumulation of the

radioactivity was observed in any particular tissue. Fat appeared to retain a small amount of the radioactivity. The slight increase in radioactivity in the kidney reflected the major excretory route of 2,4-DP acid.

The results obtained from this study provided useful information, but the study should have examined excretion and metabolism of the test compound. This study is classified as unacceptable.

TABLE 1*

Mean tissue distribution of radioactivity following daily oral administration of (^{14}C)-DICHLORPROP to the rat for a period up to 14 days at a dose level of 1 mg/kg body weight

Time after first dose (days)	Sex	Liver	Kidney	Muscle	Thyroid	Adrenal	Fat	Plasma
1	♂	0.04	0.26	0.01	0.01	0.08	0.05	0.10
	♀	0.01	0.09	<0.01	<0.01	0.01	0.03	0.04
6	♂	0.11	0.48	0.01	0.02	0.05	0.09	0.17
	♀	0.03	0.13	0.01	0.07	0.07	0.05	0.07
11	♂	0.10	0.38	0.02	0.04	0.04	0.12	0.14
	♀	0.06	0.29	0.01	0.04	0.04	0.12	0.13
15	♂	0.10	0.45	0.02	0.05	0.07	0.15	0.17
	♀	0.03	0.22	0.01	0.03	0.03	0.08	0.07
18	♂	0.04	0.10	0.02	0.01	0.02	0.07	0.05
	♀	0.02	0.10	0.01	<0.01	0.02	0.09	0.06

Radioactivity expressed in terms of µg equivalents of (^{14}C)-DICHLORPROP/g of tissue, except for plasma where it is µg equivalents/ml.
These values are the mean of two animals.

* DATA TAKEN FROM Submission; MRID No. 116493