OVERVIEW

MESOTRIONE (ZA1296) 7/18/2000

Study Type: Non-Guideline; Biochemical Studies in Rat and Mouse Liver

Work Assignment No. 2-01-52C (amend 1) (MRID 44505029)

Prepared for

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OVERVIEW

STUDY TYPE: Biochemical study-rat and mouse
OPPTS Number: N/A OPP Guideline Number: N/A

DP BARCODE: D259369 SUBMISSION CODE: S541375
P.C. CODE: 122990 TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): Mesotrione (100%)

SYNONYMS: ZA1296; 2-[4-(methylsulfonyl)-2-nitrobenzoyl]-1,3-cyclohexanedione

CITATION: Odum, J. (1997) ZA1296: Biochemical Studies in Rat and Mouse Liver. Central Toxicology Laboratory, Cheshire, UK, Laboratory Report No.: CTL/R/1339, November 14, 1997. MRID 44505029. Unpublished.

SPONSOR: Zeneca AG Products, Wilmington, Delaware

EXECUTIVE SUMMARY: In this special study, (MRID 44505029), mesotrione (100% purity and batch number Y06684/003/001) was administered for 28 days in the diet to CD rats and CD1 mice (5/group) at 1000, 3000 (mice only) 7000, or 16000 (rats only) ppm. The control animals (10/group) received control diet only. Standard cytochrome P450 (CYP) inducers were administered intraperitoneally (i.p.) for 4 days to Alpk:AP rats (3/group) and AP Swiss mice (3/group).

The objective of this study was to investigate the induction of hepatic CYP isoforms by mesotrione and compare the results with those of a series of standard CYP inducing agents including: β- naphthoflavone (BNF), phenobarbital (PB), dexamethasone (DEX), and methylclofenapate (MCP). The induction of CYP isoforms by the inducing agents was performed on Alpk:AP rats and AP Swiss mice because of animal supply problems. Food consumption, body weights, and clinical observations were performed throughout the study and at termination. Three CYP isoforms were quantified by immunoblotting. The use of monoclonal vs polyclonal antibodies for the immunoblotting assay was not specified. The specificities of the model substrates for three CYP isoforms were deduced from the effects of the standard inducers and their isoenzyme profiles after electrophoresis.

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Food consumption, body weights, and clinical signs in both species and clinical chemistry parameters in the rat were not affected by treatment with mesotrione. In mice, treatment with mesotrione produced an increase ($p<0.05$) in plasma triglycerides at 3000 (↑41%) and 7000 ppm (↑45%), a decrease ($p<0.05$) in plasma alanine transaminase (ALT) at 7000 ppm (↓23%), and slight liver hypertrophy at 3000 (2/5 animals) and 7000 ppm (4/5 animals). In rats, treatment with mesotrione produced an increase ($p<0.05$) in relative (to body) liver weights in the 1000 (↑9%) and 16000 (↑11%) ppm groups and an increase in slight centrilobular hypertrophy at 16000 ppm (4/5 treated). Treatment with mesotrione had no effect on absolute or relative (to body) liver weights in mice or total CYP in either species. In mesotrione-treated rats, increases ($p<0.05$, 0.01, or 0.001) in activity of 4 CYP enzymes were observed at 7000 ppm (↑54-141%) and 16000 ppm (28-147%). In mice, increases ($p<0.01$) were observed in the activities of one CYP enzyme in the 3000 ppm (↑253%) and in two CYP enzymes in the 7000 ppm group (↑26-189%). In the 7000 and 16000 ppm rats, CYP isoform profiles showed minimal induction relative to controls in CYP 1A1 and its associated enzyme activities. In mice, minimal induction was observed in CYP 2B1/2 (3000 and 7000 ppm groups) and CYP 3A1 (1000 and 3000 ppm groups) and their associated enzyme activity.

In rats, treatment with CYP inducers resulted in increased ($p<0.01$ or 0.001) absolute and relative liver weights. In mice, only treatment with MCP resulted in increased ($p<0.001$) absolute and relative (to body) liver weights; treatment with PB resulted in an increase ($p<0.05$) in relative liver weight. In general, the standard CYP inducers caused large increases in the activities of the CYP enzymes. The standard inducers produced moderate to marked increases in CYP 1A1, 2B1/2, and 3A1 isoform profiles of both species. BNF induced only 1A1 while PB and DEX induced both 2B1/2 and 3A1. Induction profiles for MCP were not analyzed. The results of this special study are presented as an attachment to this overview (study report Tables 1 through 9, pages 17-25).

In summary, treatment with mesotrione for 28 days resulted in slight increases in rat liver weights, slight microscopic liver hypertrophy in rats and mice, and minimal CYP induction in both species.

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