OVERVIEW

MESOTRIONE (ZA1296) 7/18/2000

Study Type: Non-Guideline; Effects of MNBA (a Mesotrione Metabolite) on HPPD activity

Work Assignment No. 2-01-52N (amend 1) (MRID 44901712)

Prepared for

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DATA EVALUATION RECORD

STUDY TYPE: Effect on HPPD activity
OPPTS Number: N/A

OPP Guideline Number: non-GDL

DP BARCODE: D259369
P.C. CODE: 122990

SUBMISSION CODE: S541375
TOX. CHEM. NO.: None

TEST MATERIAL (PURITY): MNBA (mesotrione metabolite; 97% purity)

SYNONYMS: 4-methylsulphonyl-2-nitro-benzoic acid

CITATION: Elcombe, B. M., Meadowcroft, S., (1998) ZA1296: Effects of MNBA, a Metabolite of ZA1296 on p-Hydroxyphenylpyruvate Dioxygenase (HPPD) Activity. Central Toxicology Laboratory, Cheshire, UK, Laboratory Report No: CTL/R/1367; Study No: XR6244., April 1998. MRID 44901712. Unpublished.

SPONSOR: Zeneca AG Products, Wilmington, Delaware

Executive Summary: The objective of this study (MRID 44901712) was to investigate the inhibition of p-hydroxyphenylpyruvate dioxygenase (HPPD) by MNBA (a mesotrione metabolite; 97% purity, Y08636/004/001) in isolated liver cytosol from untreated male Alpk:ApfSD rats. HPPD is involved in the catabolism of tyrosine by catalyzing the oxidative decarboxylation and rearrangement of 4-hydroxyphenylpyruvate (HPPA) to homogentisate. The liver cytosol samples were incubated with (i) MNBA at concentrations of 0.02 or 20μM, (ii) mesotrione (96.8% purity, batch P17) and NTBC (92% purity) each at concentrations of 0.02, 0.2, or 20μM (positive controls), and (iii) sodium phosphate buffer only (negative control). To assay HPPD activity, oxygen consumption rates (μL O_2/min) for background, control (negative and positive), and treated liver cytosol samples were calculated.

The results of this special study are presented as an attachment to this overview (study report Tables 1 and 2, page15). The addition of MNBA at 0.02 and 20 μM to isolated rat liver cytosol resulted in 0 and 7.2% inhibition of HPPD, respectively. The addition of mesotrione or NTBC at 0.02μM resulted in 70-78% inhibition of HPPD, while concentrations of 0.2 and 20μM resulted in 99-100% inhibition. The Sponsor stated that structure activity relationships also indicated that the metabolite will be at most a weak inhibitor of HPPD.

In conclusion, MNBA is a very weak inhibitor of HPPD *in vitro* and it appears it will not perturb tyrosine catabolism *in vivo*. A more definite conclusion cannot be reached without knowing the expected *in vivo* concentration.

ATTACHMENT

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