7/18/2000

DATA EVALUATION RECORD

MESOTRIONE

Study Type: §Non-guideline; ZA1296: Preliminary Data from a Single Oral Dosing Study in Man

Work Assignment No. 2-01-52MM (MRID 44505114)

Prepared for
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U.S. Environmental Protection Agency
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MESOTRIONE (ZA1296)

Human single oral dose (Non-Gdl)

David Nixon 7/12/2000

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DATA EVALUATION RECORD

STUDY TYPE: Oral Dosing Study in Man
OPPTS Number: None

OPP Guideline Number: §Non-guideline

DP BARCODE: D259369
P.C. CODE: 122990

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

TEST MATERIAL (PURITY): Mesotrione (99.7% a.i.)

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

CITATIONS: Hall, M.G. (1997) ZA1296: Preliminary Data from a Single Oral Dosing Study in Man. Central Toxicology Laboratory, Cheshire, UK. Laboratory Report No.: CTL/R/1352. Study No.: QH0019, December 18, 1997. MRID 44505114. Unpublished.

SPONSOR: Zeneca Ag Products, Wilmington, DE

EXECUTIVE SUMMARY: In a special study (MRID 44505114), healthy male human subjects (6/dose) were given a single oral dose of mesotrione (99.7% a.i.; Batch # Y06684/219) at 0.1, 0.5, or 4 mg/kg. Pre- and post-dosing urinalysis, hematology, and clinical chemistry parameters were measured, and a pulmonary function test, electrocardiogram, and corneal exam were performed pre-study and post-study. Plasma tyrosine levels were determined pre- and post-dosing from -72 to +96 hours of dosing.

The stated purposes of this study were to 1) identify suitable urinary markers to allow non-invasive monitoring of worker exposure to mesotrione and 2) to define the dose response for increased plasma tyrosine to mesotrione dose.

No effects were observed on hematology, clinical chemistry, or urinalysis parameters. No adverse effects were observed upon physical examination.

Dosing with mesotrione at 0.1, 0.5, or 4 mg/kg elevated plasma tyrosine starting at 2 hours post-dosing and remaining elevated until between 12 and 24 hours (0.1 and 0.5 mg/kg) or between 36 and 48 hours (4 mg/kg) post-dosing. The mean plasma tyrosine levels peaked at 5 hours post-dosing in the 0.1 mg/kg group (129 nmol/mL), at 6 hours post-dosing in the 0.5 group (152 nmol/mL), and at 8 hours post-dosing in the 4 mg/kg group (289 nmol/mL).

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At 0.1 mg/kg, plasma tyrosine maximums ranged from 91.1 to 161 nmol/mL during the 24 hour period following dosing vs. 68.6 to 106 nmol/mL during pre-dosing.

At 0.5 mg/kg, plasma tyrosine maximums ranged from 121 to 210 nmol/mL during the 24 hour period following dosing vs. 65.1 to 102 nmol/mL during pre-dosing.

At 4 mg/kg, plasma tyrosine maximums ranged from 241 to 420 nmol/mL during the 24 hour period following dosing vs. 95.3 to 127 nmol/mL during pre-dosing.

Mean AUC values were increased in a dose-dependent manner during the 24 hours immediately following dosing (day 0) with respect to the 24 hour period immediately preceding dosing (day -1): 0.1 mg/kg - (↑42%); 0.5 mg/kg - (↑84%); and 4 mg/kg - (↑130%) mg/kg subjects. For the period from 24 to 48 hours following dosing (day 1), plasma tyrosine AUC values remained slightly elevated with respect to day -1 levels (↑16%, ↑32%, and ↑27% in 0.1, 0.5, and 4 mg/kg subjects, respectively). For the periods from 48 to 72 hours (day 2) and 72 to 96 hours (day 3) following dosing, plasma tyrosine AUC values were only slightly elevated in 0.1 (↑5-7%) and 4 mg/kg (↑5-8%) treated subjects, whereas AUC values remained elevated in 0.5 mg/kg subjects (↑20-22%).

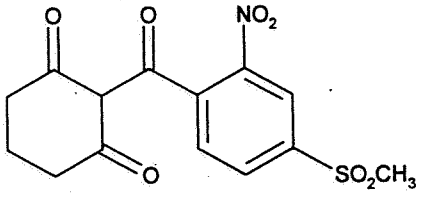
This is study is classified **unacceptable (non-guideline)** and does not satisfy the purposes for which it was intended. No data were presented regarding identifying suitable urinary markers to allow non-invasive monitoring of worker exposure to mesotrione and the dose response for increased plasma tyrosine to mesotrione dose was not analyzed statistically.

COMPLIANCE: Signed and dated GLP and Data Confidentiality statements were provided. No Quality Assurance or Flagging statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Mesotrione
   Description: White solid
   Lot/Batch #: Y06684/219
   Purity: 99.7% a.i. (w/w)
   Stability of compound: Not specified
   Storage: Approximately 4°C
   CAS #: 104206-82-8
   Structure:



2. Vehicle: Gelatin capsules

3. Test subjects: Human male volunteers
   Age and weight at the start of dosing: Between 18-55 years (inclusive); 60 to 90 kg (inclusive) and not varying more than ±20% from the desired weight.
   Source: Inveresk Clinical Research (ICR) Volunteer Panel
   Testing Facility: ICR, Edinburgh, Scotland
   Diet: Identical standard meals at comparable time points in order to minimize variability in plasma tyrosine concentrations. No caffeinated beverages were allowed from the midnight before dosing until 24 hours after dosing. No alcohol consumption was allowed for 24 hours before admission to the facility and for 5 days after dosing. Volunteers were fasted from midnight prior to dosing and for 4 hours after dosing and were allowed free access to fluids from 2 hours after dosing onward.
   Acclimation period: 4 days

B. STUDY DESIGN: This study was designed to identify suitable urinary markers to allow for monitoring of worker exposure to mesotrione and to define the dose response for increased plasma tyrosine. Mesotrione belongs to a class of compounds known as triketones which inhibit the enzyme 4-hydroxyphenyl pyruvate dioxygenase (HPPD). In mammals, HPPD is responsible for catabolism of tyrosine to 4-hydroxyphenyl pyruvic acid (HPPA); as this conversion is reversible, inhibition leads to an accumulation of tyrosine and HPPA in the body. Tyrosine is readily reabsorbed in the kidneys resulting in high systemic concentrations whereas HPPA and its metabolite 4-hydroxyphenyl lactic acid (HPLA) are readily excreted in the urine. Inhibition of HPPD results in increased concentrations of tyrosine in plasma and increased urinary elimination of HPPA, HPLA, and associated compounds (known collectively as phenolic acids).

1. In life dates: Start - 9/11/97 End - 11/6/97

2. Subject assignment: Volunteers were sequentially assigned to dose groups.

3. Dose selection rationale - It was stated that dose levels were selected based on previous studies in a range of laboratory animals and from a knowledge of previous clinical experience with a similar compound. No further information was provided.

4. Dosing preparation, analysis, and administration - The test substance was administered by gelatin capsules in a single dose. Capsules were prepared on the day of dosing using the body weights determined in the pre-study medical evaluation. Following preparation, capsules were stored at room temperature and were administered within four hours of preparation. No stability data were provided. It was stated that all doses were within 1% of the nominal values; however, no data were reported. The subjects were dosed once orally by capsule at target doses of 0.1, 0.5, or 4 mg/kg bodyweight. All volunteers were weighed prior to dosing to determine dose per subject and were fasted from midnight on day -1 to 1:00 P.M. on the day of dosing. On the day of dosing, an appropriate amount of mesotrione was administered in a gelatin capsule with 150 mL distilled water with the volunteer sitting upright. The volunteers were instructed that the capsules should be swallowed and not chewed or crushed.

5. Statistics - No statistical analyses were employed. Data were summarized as means ± standard deviation and presented graphically.

C. METHODS (see attachment of Appendix C from the study report for the study schedule):

1. Observations - Any detrimental change in the volunteer's condition subsequent to the study start and until the post-study medical examination was noted. Symptoms were recorded at 24-hours post-dosing.

2. Blood - In the pre-test medical screen, blood was collected via venipuncture for hematology and clinical chemistry parameters, hepatitis B and C antigens, and human immunodeficiency virus. At 96 hours post-dosing and at 4 to 7 days after discharge, blood was again collected for the determination of hematology and clinical chemistry parameters. The following checked (X) hematology and clinical chemistry parameters were determined:

   a. Hematology

X	Hematocrit (HCT)	X	Leukocyte differential count
X	Hemoglobin (HGB)	X	Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)	X	Mean corpusc. HGB conc.(MCHC)
X	Erythrocyte count (RBC)	X	Mean corpusc. volume (MCV)
X	Platelet count		Reticulocyte count
X	Blood clotting measurements		Erythrocyte distribution width
X	(Thromboplastin time)		
X	(Activated partial thromboplastin time)		
	(Clotting time)		
	(Prothrombin time)		

b. Clinical Chemistry

	ELECTROLYTES		OTHER
X	Calcium	X	Albumin
X	Chloride	X	Blood creatinine
	Magnesium	X	Blood urea nitrogen
X	Inorganic phosphate	X	Uric acid
X	Potassium	X	Total Cholesterol
X	Sodium	X	Globulin
		X	Glucose
	ENZYMES		Direct bilirubin
X	Alkaline phosphatase (ALK)	X	Total bilirubin
	Cholinesterase (ChE)		Total plasma protein (TP)
X	Creatine phosphokinase (CK)	X	Triglycerides
	Lactic acid dehydrogenase (LDH)		
X	Serum alanine aminotransferase (ALT)		
X	Serum aspartate aminotransferase (AST)		
X	Gamma glutamyl transferase (GGT)		
	Glutamate dehydrogenase		

Plasma samples for determination of tyrosine and ZA1296 were collected at the pre- and post-study medical evaluation, at 16 timepoints in the 3 days prior to dosing, and at 16 additional timepoints in the 4 days following dosing.

3. Urine - In the pre-test medical screen, urine was collected for standard urinalysis and drugs of abuse screen. During the dosing, urine was collected for clinical evaluation and measurement of tyrosine metabolites and parent compound; these samples were collected at 12 hourly intervals for 72 hours prior to dosing, at 4 hourly intervals for the initial 12 hours after dosing, and at 12 hourly intervals for the remainder of the 96 hours post-dosing. At 96 hours post-dosing and again at 4 to 7 days after discharge, urine was collected and standard urinalysis was performed. The following checked (X) parameters were examined:

	Appearance	X	Glucose
X	Volume	X	Ketones
X	Specific gravity	X	Bilirubin
X	pH	X	Blood
X	Sediment (microscopic)		Nitrate
X	Protein	X	Urobilinogen

4. Ophthalmoscopic examination - Corneal exams were performed at the pre- and post-study examinations.

II. RESULTS

A. Subject symptomology:

None of the subjects reported any symptoms during the study.

B. Clinical chemistry, hematology, and urinalysis:

It was stated that no clinically significant, treatment-related changes in clinical chemistry, hematology, or urinalysis parameters occurred during the study. No data were provided.

C. Vital signs, physical findings, and other safety variables:

It was stated that no clinically significant changes were observed in vital signs, physical examinations, pulmonary function tests, or electrocardiography during the study. No data were provided.

D. Ophthalmoscopic exam:

It was stated that there were no clinically significant changes observed between the pre- and post-dose ophthalmoscopic examinations. No data were provided.

E. Adverse events, subject withdrawals and drop outs:

A total of 14 adverse events were reported during the study; however, none were considered to be treatment-related.

F. Plasma tyrosine concentrations:

Dosing with mesotrione at 0.1, 0.5, or 4 mg/kg elevated plasma tyrosine (Table 1) starting at 2 hours post-dosing and remaining elevated until between 12 and 24 hours (0.1 and 0.5 mg/kg) or between 36 and 48 hours (4 mg/kg) post-dosing. The mean plasma tyrosine levels peaked at 5 hours post-dosing in the 0.1 mg/kg group (129 nmol/mL), at 6 hours post-dosing

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in the 0.5 group (152 nmol/mL), and at 8 hours post-dosing in the 4 mg/kg group (289 nmol/mL).

In subjects treated with 0.1 mg/kg mesotrione, plasma tyrosine maximums ranged from 91:1 to 161 nmol/mL during the 24 hour period following dosing (vs. 68.6 to 106 nmol/mL during pre-dosing). By 24 hours post-dosing, plasma tyrosine concentrations had returned to normal levels.

In subjects treated with 0.5 mg/kg mesotrione, plasma tyrosine maximums ranged from 121 to 210 nmol/mL during the 24 hour period following dosing (vs. 65.1 to 102 nmol/mL during pre-dosing). By 24 hours post-dosing, plasma tyrosine concentrations had returned to normal levels.

In subjects treated with 4 mg/kg mesotrione, plasma tyrosine maximums ranged from 241 to 420 nmol/mL during the 24 hour period following dosing vs. 95.3 to 127 nmol/mL during pre-dosing. Plasma tyrosine levels continued to be elevated even after 24 hours post-dosing in some subjects, but by 48 hours post-dosing, plasma tyrosine concentrations had returned to normal levels in all subjects.

Table 1. Selected mean plasma tyrosine levels (nmol/mL) in human subjects receiving a single oral dose of mesotrione at 0.1, 0.5 or 4 mg/kg.[a]

	Dosage (mg/kg)		
Study hour	0.1	0.5	4
-72	54.5	45.9	65.5
-60	64.8	71.6	74.2
-48	50.5	50.7	70.1
-36	84.8	66.0	101
-24	60.5	64.5	74.1
-18	67.9	64.2	95.5
-12	79.5	60.0	101
0	54.3	52.2	76.5
1	56.2	53.4	76.2
2	68.3	65.5	91.7
3	81.6	85.9	125
4	84.6	91.2	138
5	129	135	231
6	127	152	258
8	106	147	289
12	118	139	284
24	67.8	66.0	126
30	82.0	85.1	129
36	92.6	86.2	120
48	60.7	66.5	84.7
60	86.0	78.9	105
72	57.4	61.0	82.1
84	84.8	81.8	113
96	59.6	66.2	82.0

a Data are the mean of six subjects at each sampling interval and were obtained from Tables 1, 2, and 3, pages 45, 46, and 47 of the study report.

Area under the curve (AUC) values (Table 2) were calculated for 24 hour periods for the 3 days preceding dosing (days -3, -2, and -1), the day of dosing (day 0), and the 3 days following the day of dosing (days 1, 2, and 3). Mean AUC values were increased in a dose-dependent manner during the 24 hours immediately following dosing (day 0) with respect to the 24 hour period immediately preceding dosing (day -1): 0.1 mg/kg - (↑42%); 0.5 mg/kg - (↑84%); and 4 mg/kg - (↑130%) mg/kg subjects. For the period from 24 to 48 hours following dosing (day 1), plasma tyrosine AUC values remained slightly elevated with respect to day -1 levels (↑16%, ↑32%, and ↑27% in 0.1, 0.5, and 4 mg/kg subjects,

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respectively). For the periods from 48 to 72 hours (day 2) and 72 to 96 hours (day 3) following dosing, plasma tyrosine AUC values were only slightly elevated in 0.1 (↑5-7%) and 4 mg/kg (↑5-8%) treated subjects, whereas AUC values remained elevated in 0.5 mg/kg subjects (↑20-22%).

Table 2. Area under the curve (AUC) values of plasma tyrosine (nmol x h/mL) in human subjects receiving a single oral dose of mesotrione at 0.1, 0.5 or 4 mg/kg.[a]

	Dosage (mg/kg)		
Study Day	0.1	0.5	4
-3	1337	1364	1692
-2	1695	1486	2083
-1	1630	1431	2162
0	2307	2635	4980
1	1893	1884	2737
2	1741	1712	2261
3	1719	1745	2341
Total pre-dose (days -3, -2 ,-1)	4663	4281	5936
Total post-dose (days 0, 1, 2, 3)	5940	6231	9977

a Data are the mean of six subjects at each sampling interval and were obtained from Tables 4, 5, and 6, pages 48, 49, and 50 of the study report.

II. DISCUSSION

A. Investigator's Conclusions - The study author concluded that no adverse effects occurred following administration of a single oral dose of 0.1, 0.5, or 4 mg/kg of mesotrione. In particular, no ophthalmological changes were noted. Plasma tyrosine levels were variable, tending to increase during the day and decrease at night. At 0.1 and 0.5 mg/kg mesotrione, plasma tyrosine levels returned to background levels by 24 hours after dosing. At 4 mg/kg, plasma tyrosine levels returned to background levels by 48 hours after dosing. Both mean peak plasma tyrosine concentration and plasma tyrosine AUC values increased with increasing dose.

B. Reviewer's Discussion - In this special study, healthy male human subjects (6/dose) were given a single oral dose of mesotrione (99.7% a.i.) at 0.1, 0.5, or 4 mg/kg. Pre- and post-dosing urinalysis, hematology, and clinical chemistry parameters were measured, and a pulmonary function test, electrocardiogram, and corneal exam were performed pre-study and post-study. Plasma tyrosine levels were determined pre-dosing and post-dosing from -72 to +96 hours of dosing.

The purpose of the study was to 1) identify suitable urinary markers to allow non-invasive monitoring of worker exposure to mesotrione and 2) define the dose response for increased plasma tyrosine.

No effects were observed on hematology, clinical chemistry, or urinalysis parameters. No adverse effects were observed upon physical examination.

Dosing with mesotrione at 0.1, 0.5, or 4 mg/kg elevated plasma tyrosine starting at 2 hours post-dosing and remaining elevated until between 12 and 24 hours (0.1 and 0.5 mg/kg) or between 36 and 48 hours (4 mg/kg) post-dosing. The mean plasma tyrosine levels peaked at 5 hours post-dosing in the 0.1 mg/kg group (129 nmol/mL), at 6 hours post-dosing in the 0.5 group (152 nmol/mL), and at 8 hours post-dosing in the 4 mg/kg group (289 nmol/mL).

At 0.1 mg/kg, plasma tyrosine maximums ranged from 91.1 to 161 nmol/mL during the 24 hour period following dosing vs. 68.6 to 106 nmol/mL during pre-dosing. By 24 hours post-dosing, plasma tyrosine concentrations had returned to normal levels.

At 0.5 mg/kg, plasma tyrosine maximums ranged from 121 to 210 nmol/mL during the 24 hour period following dosing vs. 65.1 to 102 nmol/mL during pre-dosing. By 24 hours post-dosing, plasma tyrosine concentrations had returned to normal levels.

At 4 mg/kg, plasma tyrosine maximums ranged from 241 to 420 nmol/mL during the 24 hour period following dosing vs. 95.3 to 127 nmol/mL during pre-dosing. Plasma tyrosine levels continued to be elevated even after 24 hours post-dosing in some subjects, but by 48 hours post-dosing, plasma tyrosine concentrations had returned to normal levels in all subjects.

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This is study is classified **unacceptable (non-guideline)** and <u>does not</u> satisfy the purposes for which it was intended. No data were presented regarding identifying suitable urinary markers to allow non-invasive monitoring of worker exposure to mesotrione and the dose response for increased plasma tyrosine to mesotrione dose was not analyzed statistically.

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C. Study deficiencies - No stability data were provided; however, the neat test substance was administered within 4 hours of preparation.

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APPENDIX

THE FOLLOWING ATTACHMENT IS NOT AVAILABLE ELECTRONICALLY
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