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DATA EVALUATION REPORT

Study Type: 14-Day Intrathyroidal Metabolism Study
Guideline Series 85-1

EPA ID No.: MRID No.: 431350-03
Pesticide Chemical Code: 108501
Tox Chemical No.: 454BB
DP Barcode: D201875
Submission No.: S463228

Test Material: AC 92,533

Synonyms: Pendimethalin, Prowl, N-(-1-ethylpropyl)-3,4-dimethyl-2,6-dinitrobenzeneamine

Sponsor: American Cyanamid Co.
Princeton, NJ 08543-0400

Testing Facility: Division of Endocrinology, University of Massachusetts Medical School , Worchester, MA 01655

Title of Report: A 14-Day Intrathyroidal Metabolism Study in Male Rats with AC 92,553

Study Number: UM-91-06-01

Authors: William J. DeVito and Lewis E. Braverman

Report Issued: April 16, 1993

Executive Summary: In a special 14-day feeding study to determine thyroid function (MRID 43135003), AC 92,553 (Pendimethalin, 92.6%, Lot #AC5213-72A) was administered in the diet to groups of 10 male Crl:CD(SD) rats at dose levels of 0, 100 or 5000 ppm (corresponding to 0, 10 or 500 mg/kg/day).

At 5000 ppm AC 92,533 for 14 days, TSH was increased and T_4 and T_3 were decreased. No treatment related effects were observed for rT_3 levels, thyroid weight, ^{131}I uptake in MIT, DIT or T_4. There was a significant increase of ^{131}I uptake by the thyroid of rats in the 5000 ppm group and an increase in incorporation of ^{131}I in T_3. Total T_3 and T_4 levels in the thyroid were not affected by treatment at 5000 ppm. **The LOEL is 5,000 ppm (500 mg/kg/day) based on thyroid effects. The NOEL is 100 ppm (10 mg/kg/day).**

The study is **core-supplementary** and does not by itself satisfy the guideline requirement for a series 85-1 metabolism study.

A. Materials

1. Test compound: AC 92,533; Description: orange solid; Lot No.: AC 6539-77A; Purity: 92.98%, Contaminants: not reported.

2. Test animals: Species: rat; Strain: Crl: CD(SD); Age: 13 weeks, Weight: not reported; Source: Charles River Laboratories, Inc.

B. Study Design:

14-DAY INTRATHYROIDAL METABOLISM STUDY

Test Group	Dose in Diet (ppm)	Number of Rats
Control	0	10
Low	100	10
High	5000	10

Rats were maintained under "controlled" conditions with a 12 hour on/off light cycle. Rats were maintained on their respective diets for 14 days after which blood samples were obtained by retroorbital bleeding and the serum was frozen at -20 degrees C and later analyzed for serum TSH, T_3, T_4 and rT_3. Each rat then received an ip injection of 25-50 μCi ^{131}I(NaI). Two hours after injection, the rats were sacrificed and blood was collected. One 50 μl aliquot was counted. A 10-20 μl aliquot was subjected to paper electrophoresis. The percentage of ^{131}I present in the organic forms was determined by counting the appropriate zones by autoradiography. An aliquot of homogenate from each thyroid was hydrolyzed with 20 mg of pancreatin at 37 degrees C. Then the homogenate was subjected to ascending paper chromatography in butanol-ethanol-0.5 N ammonia (5:1:2) solvent system. Monoiodotyrosine (MIT), diiodotyrosine(DIT), T3, and T4 were localized and counted. At termination, body weight and thyroid weight were determined.

C. Results

There was a significant increase in TSH (60%) in the 5000 ppm group when compared to the control and 100 ppm groups. In the 5000 ppm group there were significant decreases in T_4 (80%) and T_3 (39%). No treatment related effects were noted on rT_3 or

thyroid weight. There was an increase in ^{131}I uptake in rats in the 5000 ppm group (73%) when compared to controls (see Table 1). There were no significant increases of ^{131}I uptake in MIT, DIT or T_4. There was a significant percentage of ^{131}I incorporation into T_3 in rats fed 5000 ppm AC 92,553 (see Table 2). Ingestion of 5000 ppm did not significantly affect the total concentration of T_3 or T_4 in the thyroid.

Table 1. Thyroid Function at 14 Days

Parameter	Dose Level (ppm) 0	100	5000
TSH (μU/ml)	46.04 ±21.39	41.07 ±18.08	73.82 ±33.90
T_4 (μg/dl)	5.23 ±1.02	4.12 ±1.00	1.02 ±0.28
T_3 (ng/ml)	96.42 ±20.85	76.66 ±19.07	58.40 ±13.15
rT_3 (pg/ml)	70.92 ±17.83	63.01 ±16.72	48.52 ±9.76
^{131}I uptake % dose	2.75 ±1.04	2.85 ±1.06	4.75 ±0.63
Thyroid Wt. (mg)	27.85 ±7.66	26.67 ±3.67	26.27 ±4.24

D. Discussion

Oral exposure of rats to 5000 ppm AC 92,533 increased TSH, and decreased T_4 and T_3 levels. No treatment related effects were observed for rT_3 levels, thyroid weight, ^{131}I uptake in MIT, DIT or T_4. There was a significant increase in incorporation of ^{131}I in T_3. Total T_3 and T_4 levels in the thyroid were not affected by treatment at 500 ppm. No treatment related effects were noted in the 100 ppm group.

The study is **core-supplementary.** It does not by itself satisfy the guideline requirement for a series 85-1 metabolism study.

Table 3. Percentage ^{131}I incorporated into organic ^{131}I, and ^{131}I labeled MIT, DIT, T_3 and T_4 in rats fed either control diet or diet containing 100 or 5000 ppm AC 92,553 for 14 days.

	Percentage of intrathyroidal ^{131}I		
	Control	AC 92,553 100 ppm	AC 92,553 5000 ppm
Organic ^{131}I	92.8 ± 0.9	92.8 ± 1.5	92.4 ± 1.1
MIT	33.9 ± 1.1	31.4 ± 1.1	29.8 ± 0.8
DIT	43.6 ± 1.4	44.3 ± 1.7	46.4 ± 1.5
T_3	0.37 ± 0.09	0.32 ± 0.07	1.1 ± 0.1*
T_4	1.5 ± 0.3	1.4 ± 0.2	1.2 ± 0.1

Mean ± SEM
*P <0.05 vs control and 100 ppm

Taken from p.17 of the study report.