5-20-85

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MEMORANDUM:

004463

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Registration #s: 239-1246, 239-2351; Captan;
Registration amendment #239-912, miscellaneous
toxicity data.

Tox. Chem. No.: 159
Accession No.: 251394, 251407

TO: H. Jacoby (PM 21)
Registration Division (TS-767C)

FROM: Marion P. Copley, D.V.M. Marion Copley 5/20/85
Section VI, Toxicology Branch
Hazard Evaluation Division (TS-769C)

THRU: Jane Harris, Ph.D., Section Head JEH 5/20/85
Section VI, Toxicology Branch
Hazard Evaluation Division (TS-769C)
and
Theodore M. Farber, Ph.D., Branch Chief
Toxicology Branch
Hazard Evaluation Division (TS-769C)

Chevron has submitted data and cited data to support label amendment reg. no. 239-912 for ORTHOCIDE®66 Seed Protectant.

CONCLUSIONS: The requested amendment to the label (see attached) does not appreciably alter the exposure to Captan, therefore Toxicology Branch has no objections to the proposed label changes.

1. The mutagenesis studies (see attached list) are by IBT and have previously been ruled core-invalid.

2. The rat metabolism study is unacceptable due to incomplete data presentation.

° Individual rat data is needed for the following parameters in order to consider upgrading this study to acceptable:
1) radiocarbon recovered on days 1, 2, and 3 in urine and feces
2) tissue analysis of Captan equivalents
3) metabolite quantification of the urinary metabolites
4) fecal metabolite information if available should also be sent

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- This study satisfies only part of the metabolism requirements. Single high dose and multiple low dose metabolism still need to be submitted.

- Any data derived from the companion rat metabolism study using THPI-^{14}C=O or THPI-^{14}C=epoxide should be submitted.

- A companion toxicity study using several metabolites was discussed. There was not enough information presented in order to determine the merit of the study. Any data derived from this study should be submitted to the Toxicology Branch for review.

3. A Registration Standard is being prepared for Captan, and a Special Review is currently underway. The adequacy of the existing toxicity data base will be addressed in the Registration Standard.

4. Toxicology Branch will not consider actions that significantly increase the exposure to Captan until the data gaps have been identified in the Registration Standard.

Copley, Disc 12, Doc.4, Captan, #159, Ln.53, 5/16//20/85

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Captan Science Reviews

Page _____ is not included in this copy.

Pages __3__ through __6__ are not included in this copy.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product inert impurities.

_____ Description of the product manufacturing process.

_____ Description of product quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

__X__ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action

_____ FIFRA registration data.

_____ The document is a duplicate of page(s) _____

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

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CHEVRON Captan Technical

EPA Reg. No. 239-1246

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MPC 5/20/85

Reviewed by: Marion P. Copley, D.V.M. (TS-769C)
Section VI, Tox. Branch

Secondary reviewer: Jane Harris, Ph.D. JRH 5/20/85
Section VI, Tox. Branch

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DATA EVALUATION REPORT

STUDY TYPE: Metabolism - Rat TOX. CHEM. NO.: 159

ACCESSION NUMBER: 251394, 251407

TEST MATERIAL: Captan

SYNONYMS: N-(trichloromethylthio)-1,2-dicarboximido-^{14}C-4-cyclohexene

STUDY NUMBER(S): none listed

SPONSOR: Stauffer Chemical Company

TESTING FACILITY: Stauffer Chemical Company, Mountain View, Cal.

TITLE OF REPORT: Metabolism of N-(trichloromethylthio)-1,2-dicarboximido-^{T4}C-4-cyclohexene

AUTHOR(S): L.J.Hoffman, J.R.DeBaun, J.Knarr and J.J.Menn

REPORT ISSUED: May 15, 1973

CONCLUSIONS:

1. Captan is rapidly degraded and eliminated
2. It does not bioaccumulate
3. The major route of excretion for the metabolites is urine
4. Feces is a minor route of excretion
5. Metabolites are not expelled in expired air

Classification: unacceptable due to incomplete data presentation

MATERIAL:

1. N-(trichloromethylthio)-1,2-dicarboximido-^{14}C-4-cyclohexene; (Captan-^{14}C=O), sp. act. 0.3 mCi/mMole, radiopurity >98 %.
2. Vehical - aqueous solution of 1 % tragacanth gum/0.05 % Tween-20.
3. Simonsen albino rats, male and females, 8 weeks old.

METHODS: Male and female rats were given Captan-^{14}C=,(82 mg/kg) by gavage. Two of each sex were sacrificed 1, 2, 4 and 8 days later. Rats for the 4 day sacrifice were placed in glass/stainless steel metabolism cages with expired air traps to collect expired $^{14}CO_2$. The remaining animals were placed in plastic metabolism cages. Feces, urine and expired air traps were collected and frozen until analysis. After sacrifice by cervical transection, the following tissues were weighed and frozen: blood, brain, fat (around the vas deferens), gonads, hide, kidneys, liver, lung, gastrocnemius muscle, stomach, intestine, and carcass. Feces, urine and CO_2 traps were radioassayed by liquid scintillation counting for total radioactivity. Zero to 48

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hour urine was analyzed for organo-soluble and water soluble Captan-^{14}C=O metabolites. The water soluble phase was also incubated with B-glucuronidase or B-glucuronidase:aryl sulfatase to check for glucuronide or sulfate conjugation.

Companion Metabolism Study - Two male rats were dosed with metabolites THPI-^{14}C (P.O.) or THPI-^{14}C-epoxide (I.P.) and housed in plastic metabolism cages for urine and fecal collection at 24 hours (see RESULTS for chemical formulas). Total radicactivity was assessed and urine was compared chromatographically to similar fractions from the main Captan-^{14}C=O study.

RESULTS: Elimination and distribution: The report states that by 48 hr about 92 % of the radioactivity had been excreted, mostly in the urine (80-90 %) and feces (5-15 %). This data however, are only presented by graph. There is no individual animal data. By 96 hours, 96.8 $\pm$ 1.96 % was recovered in the excreta (see attached table 1*). Radiolabelled CO_2 was not found in the expired air traps. At 96 hours the tissue residues accounted for about 1 % of the initial dose. Tissue levels (see attached table 2*) decreased rapidly to 5% of day 1 levels. They had less than 1 PPM Captan equivalents/tissue (except for blood) by 96 hours. Again no individual animal information was presented. Blood was 0.49 PPM Captan equivalents by 8 days. The report states that male and female elimination rates were not significantly different. There was no data however to support this.

Metabolites: See table 3* for the structure and amount present in the excreta of these metabolites. The following metabolites were identified in the organo-soluble phase (about 50 % of the urinary radioactivity) of the 0-4 day urine:

Metabolite 51-2 (THPI) = cis-1,2-dicarboximido-4-cyclohexene

Metabolite 51-3 (THPI-epoxide) = cis-1,2-dicarboximido-4,5-epoxy-cyclohexane

Metabolite 51-4 (trans-3-OH-THPI) = trans-1,2-dicarboximido-3-OH-4-cyclohexene; (33.4 %)

Metabolite 51-4b (5-OH-THPI) = trans-1,2-dicarboximido-5-OH-4-cyclohexene

Product 51-1, appeared to form spontaneously in the chromatoplates from metabolite 51-4.

The following metabolites were identified in the water-soiuble phase (about 50 % of the urinary radioactivity) of the 0-4 day urine:

Metabolite 53-1 (trans-3-OH-THPI)(5 %) = metabolite 51-4

Metabolite 53-2 (4,5-diOH-THPI) = cis-1-carboxy-2-carboximido-4,5-dihydroxy-cyclohexane

Metabolite 53-3 (THPAM) = cis-1-carboxy-2-carboximido-4-cyclohexene

Metabolite 53-4 (trans-3-OH-THPAM) = trans-1-carboxy-2-carboximido-3-OH-4-cyclohexene

Metabolite 53-5 is a minor, unidentified constituent of the water phase

Enzymatic hydrolysis of the urine suggested the absence of conjugated metabolites. There was no parent Captan present in the urine.

Companion Metabolism Study - Data for this study was not presented. The report stated that 95 % of the radiolabel for rats treated with either metabolite (THPI-^{14}C=O or THPI-^{14}C=epoxide epoxide) was excreted within 24 hours (90 % present in the urine). When rats were treated with THPI-^{14}C=epoxide, 60 % of the radiolabel was organo-soluble. The major metabolite was the unchanged epoxide. A minor metabolite did not cochromatograph with the urinary metabolites from the main study. The metabolites of THPI-^{14}C=O were similar to the urinary metabolites from Captan-^{14}C=O.

DISCUSSION: There are several major deficiencies in this study. There is no individual rat data for: 1) radiocarbon recovered on days 1, 2, and 8 in urine and feces; 2) tissue analysis of Captan equivalents; 3) metabolite quantification of the urinary metabolites. Without this additional information the animal to animal and male to female variation can not be determined. Too few animals were performed per sex to be confident with the quantification unless the variation is small. The authors used (±) in table 2 of the report, however thay do not say what statistic this refers to, S.D. or S.E. The authors' conclusion that male and female rats have the same metabolic pathway for Captan, cannot be supported without individual rat data for the other days of sacrifice. Although the metabolites present in the urine were studied, no analysis of the fecal metabolites was made.

Qualitative observations can be drawn from this experiment. This compound is rapidly metabolized and excreted from the body. By day 4. better than 95 % appears to be eliminated. The major route of excretion is the urine, feces to a lesser degree and no detectable elimination in the expired air. Tissue levels decrease rapidly after day one to less than 1 % by day 8, indicating no bioaccumulation. Differences between male and female tissue distribution, if any, can not be determined without the individual rat data as discussed previously.

The attached figure* indicates that the most probable metabolic pathways for Captan. The initial alteration is hydrolytic cleavage of the side chain to form THPI and trichloromethylthio moieties. THPI is the precursor for the four subsequent pathways. The major pathway appears to be hydroxylation of THPI at the 3 carbon which is metabolized into 3-OH-THPAM. Alternate pathways are shown in the attached figure*.

This study only examined a single treatment with approximately 82 mg/kg. Single high dose and multiple low dose metabolism experiments required by the U. S. Environmental Protection Agency were not studied.

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questions or comments:

- Individual rat data is needed for the following parameters in order to consider upgrading this study to acceptable:
  1. radiocarbon recovered on days 1, 2, and 8 in urine and feces
  2. tissue analysis of Captan equivalents
  3. metabolite quantification of the urinary metabolites
  4. fecal metabolite information if available should also be sent

- This study only satisfies part of the metabolism requirements. Single high dose and multiple low dose metabolism still need to be submitted.

- Any data derived from the companion metabolism study using THPI-^{14}C=O or THPI-^{14}C=epoxide should be submitted.

- A companion toxicity study using several metabolites was discussed (see attached table 4*). There was not enough information presented in order to determine the merit of the study. Any data derived from this study should be submitted to the Toxicology Branch for review.

*Tables and the figure were taken from the original report.

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TABLE 1

ible 2. Radiocarbon recovered, as % administered dose in 96 hrs, from male and female rats dosed with Captan-^{14}C=O.

	Rat Number				
mple	1	2	3	4	Average
ine	88.3	69.1	92.0	88.6	84.5
ces	8.5	25.2	7.1	8.4	12.3
pired Air	-	-	-	-	-
ssues	<0.1	<0.1	<0.1	<0.1	<0.1
Totals	96.9	94.4	99.2	97.1	96.8 ± 1.96

TABLE 2

Table 3. Radiocarbon[1] recovered in tissues and organs of rats following oral administration of Captan-^{14}C=O expressed as PPM Captan equivalents.

SAMPLE	ANALYSIS INTERVAL			
	1 Day	2 Day	4 Day	8 Day
Blood	21.80	1.97	1.32	0.49
Brain	13.80	0.47	0.20	0.13
Fat	7.05	0.00	0.00	0.00
Gonad	21.90	0.80	0.28	0.10
Hide	5.47	2.17	0.88	0.37
Intestine	34.80	2.83	0.46	0.00
Kidney	42.90	1.22	0.58	0.28
Liver	17.70	1.50	0.63	0.20
Lung	14.50	0.91	0.29	0.41
Muscle	6.30	0.50	0.22	0.20
Carcass	7.67	0.48	0.06	0.00

Table 4. Structure assignment and % distribution of Captan-^{14}C=O rat and goat urinary metabolites

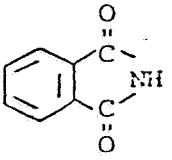
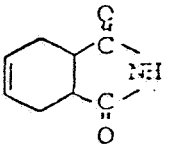
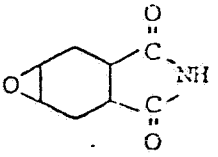
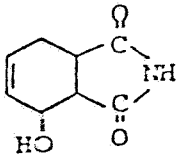
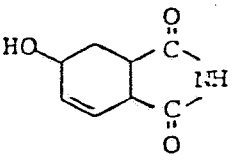
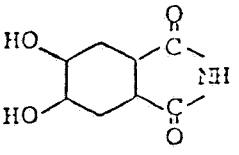
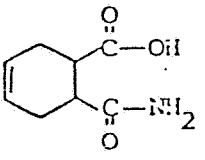
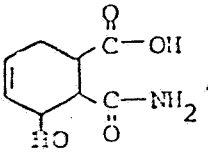
Metabolite No.	Structure Identification	% Urinary Radiocarbon Rat	Goat
51-1		0.4	0.2
51-2		15.0	0.7
51-3		5.2	1.9
51-4, 53-1		38.4	4.6
51-4b		10.1	0.7
53-2		10.9	0.0
53-3		11.7	8.1
53-4		7.1	35.1
53-5	UNKNOWN	1.2	43.7
		100.0	100.0

TABLE 4

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Table 5. Comparative toxicity values for Captan, metabolites, and related compounds.

Compound	Rat Oral	House Fly	Gambusia affinis
		(mg/kg)	(PPM)
Captan	8400	>1000	>10
Captan-epoxide	-	>1000	>10
THPI	1671	>1000	>10
THPAM	-	>1000	>10
THPI-epoxide	3160	>1000	>10
4,5-diOH-THPI	-	>1000	>10
3-OH-THPI	-	>1000	>10
3-OH-THPAM	-	>1000	>10

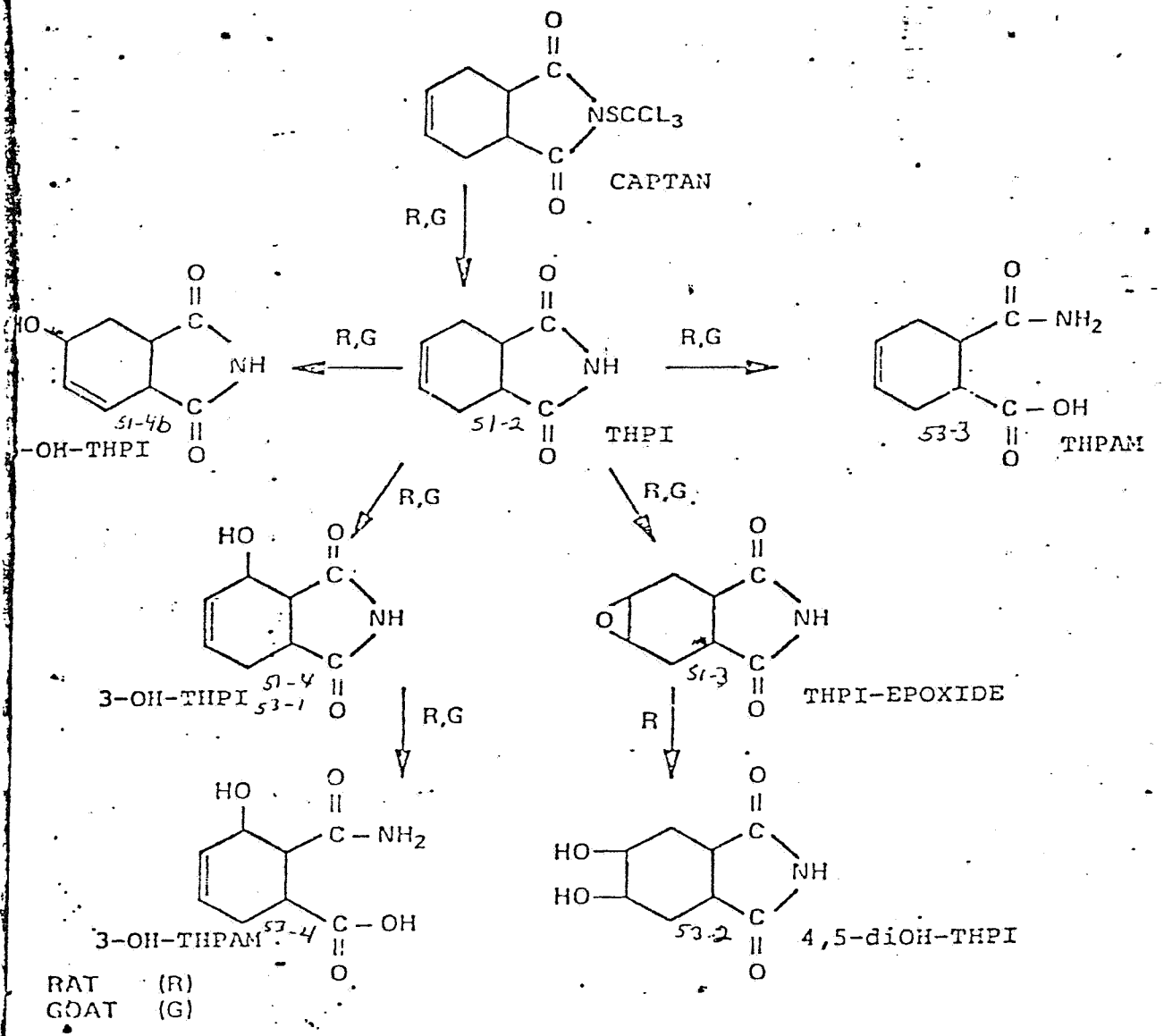

FIGURE 8 METABOLIC PATHWAY FOR CAPTAN – $^{14}C{=}O$ IN THE RAT AND GOAT