TAK-6925

NOV 7 1988

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

006925
006925

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: EPA ID 239-1246:Captan: Review rat metabolism study.

TO: Richard Mountford (PM 23)
Registration Division (TS-767C)

FROM: Marion P. Copley, D.V.M., Acting Section Head
Section 2, Toxicology Branch I (IRS)
Health Effects Division (TS-769C)

THRU: Judith W. Hauswirth, Ph.D., Acting Branch Chief
Section 2, Toxicology Branch I (IRS)
Health Effects Division (TS-769C)

Tox. Chem. No.:159
Proj. No.:8-0950
Record No.:225636

Toxicology Branch has been requested to review a rat metabolism study (#HLA 6183-107) that was submitted in support of the registration of captan technical.

CONCLUSIONS:

This study investigating the metabolism of the trichloromethylthio moiety of captan is acceptable (see comment 1 and Data Evaluation Report - DER is attached), however the guideline requirements (85-1) have not been completely satisfied due to deficiencies in the evaluation of the metabolism of the tetrahydrophthalimide (THPI) moiety (see comment 3).

BACKGROUND:

Captan is currently undergoing Special Review. Position Document (PD) 2/3 was completed in June, 1985. The Toxicology Branch Peer Review Committee determined that Captan is a B_2 oncogen (12/29/86). The following data gaps identified in the Registration Standard for Captan (March 1986) still remain:

- Chronic (oral) - non-rodent
- Subchronic inhalation - rat (new study to be conducted)

1 of 39
1

* Metabolism (THPI moiety) (discussed in comments 1, 3 and DER)

COMMENTS

1. Summary of metabolism study number HLA 6183-107 (see attached DER)

Captan, with a radiolabel on the side chain (trichloromethylthio moiety), was administered to rats at single doses of 10 or 500 mg/kg. In addition, a group of rats received 10 mg/kg of radiolabelled captan following 14 days of cold captan (pretreatment).

Conclusions are:

* Captan radiolabel (dose 10 mg/kg - single and loaded) was rapidly excreted, 77-84 % within 24 hours, primarily in the urine, secondarily in the CO_2 and feces.

* Following the pretreatment, feces were the primary route of elimination.

* Parent compound was not found in the urine, but accounted for about 2 % of the fecal radioactivity in rats receiving the high dose.

2. The results of this study compare favorably to those of previously submitted journal articles.

3. In order to satisfy the guideline requirements, acceptable studies evaluating the metabolism, distribution and elimination of captan at single low and high and repeated doses for both the:

1) THPI (ring) and
2) trichloromethylthio (side chain) moieties

are required.

Although the attached study satisfies the guideline requirements concerning metabolism of the side chain, metabolism data for the THPI moiety however is incomplete for the following reasons:

1) Although much metabolism data is available in the literature, there are currently no core-acceptable metabolism studies conducted with a THPI label.

2) A study submitted previously by the Registrant (see memorandum from M. Copley to H. Jacoby dated 11/5/86,TB doc 005571) was classified core-supplementary since the scope was limited to investigation of effects in the gastrointestinal tract of rats and mice.

Therefore, a study investigating the metabolism, distribution and elimination of captan with a ring label (THPI) is still required.

COPLEY, PC6\CAPTAN\MEMO1.224, #159, 11/7/88

006925

EPA: 68D80056
DYNAMAC No.: 120-A
October 19, 1988

DATA EVALUATION RECORD

CAPTAN

Metabolism Study in Rats

STUDY IDENTIFICATION: Dawn, R. J. Evaluation of the in vivo metabolism of captan in rats. (Unpublished study No. HLA 6183-107 performed by Hazleton Laboratories America, Inc., Madison, WI, and submitted by Chevron Chemical Company, Richmond, CA; dated June 3, 1988.) MRID No. 406580-01.

APPROVED BY:

Robert J. Weir, Ph.D.
Acting Department Manager
Dynamac Corporation

Signature: Robert J. Weir

Date: 10-19-88

64

1. CHEMICAL: Captan, N-trichloromethylthio-4-cyclohexene-1, 2-dicarboximide.

2. TEST MATERIAL: [Trichloromethyl-^{14}C]Captan with a radiochemical purity of 98 percent and a specific activity of 38 mCi/μmol was used in this experiment. Unlabeled captan from lot No. 5722-43 and with a chemical purity of 99 percent was also used.

3. STUDY/ACTION TYPE: Metabolism in rats.

4. STUDY IDENTIFICATION: Dawn, R. J. Evaluation of the in vivo metabolism of captan in rats. (Unpublished study No. HLA 6183-107 performed by Hazleton Laboratories America, Inc., Madison, WI, and submitted by Chevron Chemical Company, Richmond, CA; dated June 3, 1988.) MRID No. 406580-01.

5. REVIEWED BY:

Nicolas P. Hajjar, Ph.D.
Principal Reviewer
Dynamac Corporation

Signature: Nicolas P. Hajjar
Date: October 19, 1988

William L. McLellan, Ph.D.
Independent Reviewer
Dynamac Corporation

Signature: William L. McLellan
Date: October 19, 1988

6. APPROVED BY:

I. Cecil Felkner, Ph.D.
Metabolism Studies
Technical Quality Control
Dynamac Corporation

Signature: I. Cecil Felkner
Date: 10-19-88

Marion Copley, D.V.M., D.A.B.T.
EPA Reviewer/Acting Section Head, Section 2
Toxicology Branch I (IRS)

Signature: Marion Copley
Date: [illegible]

Judith Hauswirth, Ph.D.
Acting EPA Branch Chief,
Toxicology Branch I (IRS)

Signature: Judith W. Hauswirth
Date: 11/7/88

5

7. CONCLUSIONS:

A. The metabolism of [trichloromethyl-^{14}C]captan was studied in male and female Sprague-Dawley rats following oral administration of a single dose at 10 or 500 mg/kg. In addition, the metabolism of [^{14}C]captan was studied following administration of nonradiolabeled captan at 10 mg/kg/day for 14 days; [^{14}C]captan was administered on day 15 at 10 mg/kg. Total recovery of [^{14}C] was approximately 90 percent 96 hours after administration of a single dose of captan at 10 mg/kg with about 77 to 84 percent eliminated within 24 hours postdosing. Approximately 45-50 percent of the administered dose was eliminated in the urine, 14-22 percent in the feces, and 22 to 25 percent as [^{14}C]carbon dioxide ([^{14}C]CO_2). About 1.75 percent of the dose was found in tissues, with the highest residues detected in the liver (0.27 percent), whereas only 0.14 percent was found as organic volatiles. The metabolism of [^{14}C]captan following repeated dosing at 10 mg/kg was similar to that observed following a single dose at 10 mg/kg. This finding suggests that captan is not an inducer of liver enzymes.

Following administration of 500 mg/kg [^{14}C]captan, the cumulative elimination of [^{14}C] increased gradually, reaching a maximum by 72 hours. Most of the radicactivity was eliminated in the feces (33 to 40 percent of the dose) 120 hours postdosing with lesser amounts in the urine (22-27 percent) and [^{14}C]CO_2 (15 percert). Tissue residues accounted for 0.9 percent, whereas volatile material accounted for 4 to 7 percent of the dose, a significant increase when compared to the low dose. Total recovery of [^{14}C] of the high dose accounted for 83 percent of the dose. Thiazolidine-2-thione-4-carboxylic acid (TTC) and dithiobis-methane sulfonic acid (DMS) and its monosulfoxide (DMS-O) were detected in urine. Twice as much DMS was detected in urine from female rats (50 percent) when compared to males (24 and 28 percent of the high- and low-dose rats, respectively). DMS-O accounted for about 32-38 percent in males and about 14-20 percent in females. Unchanged captan was not found in the urine, but accounted for about 2 percent of the fecal radioactivity in rats receiving the high dose.

B. This study is acceptable and meets EPA guidelines.

Items 8 through 10--see footnote 1.

11. MATERIALS AND METHODS (PROTOCOLS):

A. Materials and Methods: (See Appendix A for details.)

1. Dosing suspensions of [^{14}C]captan were prepared by mixing the appropriate amount of [^{14}C]captan and nonradiolabeled captan in 0.5 percent Tween 80 and 0.7 percent carboxymethyl cellulose in demineralized water. The dosing suspensions were stirred until used.

2. Male and female Crl:CD(SD)BR rats were obtained from Charles River Laboratories, Wilmington, MA, and acclimated to laboratory conditions for 9 to 13 days prior to dosing. The body weights of males ranged from 221 to 327 g and those of females ranged from 168 to 208 g; the age of the animals was not specified.

3. The animals were divided into three groups, each containing five per sex. Group A animals received a single oral dose of [^{14}C]captan at 10 mg/kg. Group B animals received a single daily dose of unlabeled captan at 10 mg/kg/day for 14 days, followed by 10 mg/kg [^{14}C]captan on day 15. Group C animals were dosed at 1000 mg/kg, but the experiment was repeated at a lower dose of 500 mg/kg (Group D) because it was not possible to maintain the homogeneity of the dosing solution at the higher dose.

4. Following dosing, the rats were housed individually in glass metabolism chambers for separate collection of expired CO_2, organic volatiles, urine, and feces. Food and water were available ad libitum throughout the study. Urine and feces were collected during the following time intervals after dosing: 0-6, 6-12, 12-24, 24-36, 36-48, 48-72, 72-96 (all groups), and 96-120 hours (Group D). The metabolism cages were rinsed with methanol at the time of sacrifice. Expired CO_2 and organic volatiles were collected separately at 0-6, 6-12, 12-24, 24-36, and 36-48 (all groups), and 48-72 (Group D) hours after dosing. The rats were sacrificed at 96 (Groups A, B, and C) or 120 (Group D) hours after dosing. A blood sample and a total of 14 tissues (and carcass) were collected at sacrifice.

---

[1] Only items applicable to this DER have been included.

7

5. All samples were analyzed in duplicate. Whole blood was combusted and then radioassayed by liquid scintillation counting (LCS). Feces and tissues (except bones and ovaries, which were combusted directly) were homogenized, and aliquots were combusted prior to radioanalysis. Aliquots of urine and CO_2 trapping were radioassayed directly. Organic volatiles were divided into three portions and combusted in a Harvey biological sample oxidizer and then radioassayed.

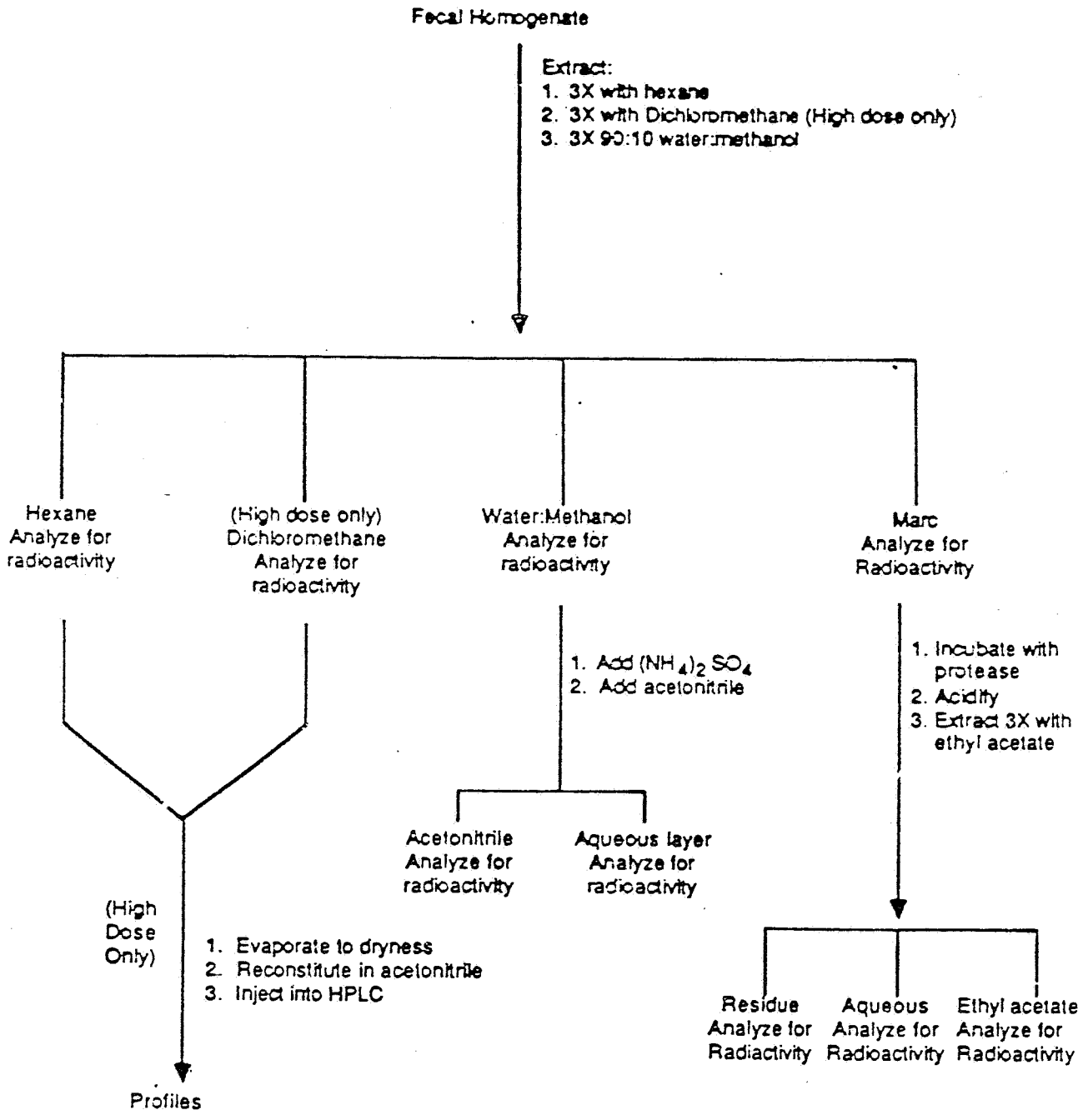
6. Characterization of [^{14}C] residues in urine was conducted by high-performance liquid chromatography (HPLC) and by thin-layer chromatography (TLC). Various urine samples were analyzed directly by these methods without prior treatment.

   Several procedures were used to analyze the feces. The best approach for feces from Group A involved three extractions with hexane, followed by three extractions with 4 mL of water:methanol (90:10). The extracts and residues were analyzed for radioactivity by LSC. An outline of the procedure is shown in Figure 1. Water:methanol extracts were mixed with an equal volume of acetonitrile and the acetonitrile was salted out with ammonium sulfate. The acetonitrile layer was analyzed by HPLC. In addition, an aliquot of the water:methanol extracts was diluted to 50 mL with water and applied to an XAD-2 column. The column was washed with 50 mL of water and eluted with 2 x 50 mL portions of methanol. The methanol fraction was analyzed by HPLC. The water fraction was applied to a Sephadex G-10-120 column and eluted in water. Eluents were then radioassayed. Fecal homogenates from the high-dose animals were analyzed in the same manner except for three extractions with 5 mL of dichloromethane following hexane extraction (Figure 1).

7. The [^{14}C] organic volatiles from Group C animals were analyzed by mass spectrometry.

B. Protocol: A protocol for this study is presented in Appendix A.

Figure 1. Definitive Method for Feces Extraction



Source: CBI Figure 39, CBI p. 127

006925

12. REPORTED RESULTS:

A. Group A: Following oral administration of [^{14}C]captan, most of the radioactivity was eliminated within 24 hours, accounting for 77.4 percent of the dose in males and 84.3 percent in females. Ninety-six hours after dosing, about 90 percent of the dose in both males and females was recovered (Table 1). Most of the radioactivity was eliminated in the urine, followed by [^{14}C]CO_2 and then feces. Less than 1 percent was found in volatiles and cage washes. Tissue residues accounted for 1.75 percent of the dose, with the highest residues found in liver (about 0.5 µg/kg; or 0.27 percent of the dose) and carcass (0.15 µg/g; or 1.05-1.26 percent of the dose) (Table 2).

B. Group B: Similar results were obtained for rats administered 10 mg/kg of [^{14}C]captan following administration of unlabeled material at the same dose daily for 14 days (Tables 1 and 2) when compared to Group A.

C. Group D: Following administration of [^{14}C]captan at 500 mg/kg, approximately 24 and 21 percent of the dose was eliminated within the first 24 hours in males and females, respectively. Thereafter, elimination of [^{14}C] increased at approximately the same rate, reaching a maximum by 72 hours after dosing. Most of the radioactivity was eliminated in the feces by 120 hours postdosing, accounting for 40 and 33 percent of the dose in males and females, respectively (Table 1). Approximately 23-27 percent of the dose was eliminated in the urine and 15 percent as [^{14}C]CO_2 in expired air. Tissue residues accounted for about 0.9 percent of the dose with the highest residues found in liver (9.9 ppm or 0.11 percent in males and 11.4 ppm or 0.1 percent in females; see Table 2). [^{14}C] residues in the carcass accounted for about 0.6 percent of the dose in both males and females. A significant increase was noted in the amounts of volatile materials released when compared to the low dose. About 3.6 and 6.7 percent of the dose was eliminated by males and females receiving 500 mg/kg, respectively, as volatiles. Total recovery of [^{14}C] accounted for 83 percent of the dose in both males and females.

TABLE 1. Material Balance of Total Radioactivity Recovered Following Oral Administration of [Trichloromethyl-^{14}C]Captan to Rats

Sample	[^{14}C]Recovered as a percent of dose administered		
	10 mg/kg[a]	10 mg/kg[a,b]	500 mg/kg[c]
		Males	
Carbon dioxide	22.01	23.54	14.45
Feces	21.51	17.58	40.14
Tissues	1.73	1.63	0.90
Urine	44.56	47.50	22.73
Volatiles	0.13	0.53	3.59
Cage wash	0.43	0.72	1.34
Cage wipe	0.17	0.32	0.14
Total	90.54±2.89	91.80±1.50	83.28±1.96
		Females	
Carbon dioxide	24.51	26.31	14.88
Feces	13.59	19.47	32.92
Tissues	1.75	1.61	0.86
Urine	50.20	40.87	27.26
Volatiles	0.14	0.26	6.66
Cage wash	0.40	1.86	0.66
Cage wipe	0.07	0.78	0.13
Total	90.66±9.27	91.7±1.15	83.37±2.84

[a] Total recovery after 96 hours postdosing.
[b] Repeated dosing.
[c] Total recovery after 120 hours postdosing.

11

TABLE 2. Radiolabeled Tissue Residues in Rats following Oral Administration of [Trichloromethyl-^{14}C]Captan

Tissue	µg equivalents/g tissue					
	10 mg/kg[a]		10 mg/kg[a,b]		500 mg/kg[c]	
Blood	0.14	0.14	0.17	0.14	4.36	6.45
Bone	0.14	0.15	0.13	0.13	2.93	3.23
Brain	0.06	0.08	0.09	0.08	1.87	2.43
Carcass	0.14	0.15	0.15	0.14	3.81	3.67
Fat	0.06	0.06	0.05	0.07	2.27	1.93
Heart	0.12	0.13	0.16	0.17	4.71	6.63
Kidney	0.61	0.61	0.73	0.63	11.20	16.20
Large Intestine w/ contents	0.10	0.11	0.17	0.14	2.57	3.74
Liver	0.48	0.51	0.40	0.40	9.90	11.40
Lungs	0.18	0.22	0.23	0.24	4.92	7.03
Muscle	0.11	0.12	0.09	0.09	2.88	2.71
Small Intestine w/ contents	0.11	0.14	0.16	0.15	2.53	3.80
Spleen	0.18	0.26	0.30	0.30	4.83	6.62
Stomach w/ contents	0.17	0.33	0.36	0.44	11.10	19.40
Gonads	0.11	0.17	0.15	0.22	3.81	7.67
Uterus	--	0.25	--	0.20	--	6.21

[a] Total recovery after 96 hours postdosing.
[b] Repeated dosing.
[c] Total recovery after 120 hours postdosing.

12

D. The results of HPLC analysis of urine samples from one male and one female at the 0- to 6-hour collection for Group A and the 0- to 6-and 24- to 36-hour collections for Group D are presented in Table 3. Two major radioactive peaks were identified as TTC and a mixture of DMS and its monosulfoxide (DMS-O). There were two minor metabolites; one eluted at the solvent front and the other at 18 to 19 minutes. The metabolic pattern was the same in all samples analyzed.

TLC analyses confirmed the presence of TTC using an authentic standard and partially resolved the sulfonic acids as suggested by comparison to published Rf values. The data indicated a clear sex-related difference in the relative proportions of DMS and DMS-O. In urine from male rats, DMS and DMS-O accounted for 24.4 and 31.8 percent of the radioactivity for Group D, respectively, and 28.0 and 38.4 percent, respectively for Group A. The corresponding values in females were 43.3 and 14.3 percent for Group D and 49.7 and 20.4 percent for Group A, respectively.

In feces of rats at the low dose, very little radioactivity was found in the hexane extract, 0.4 percent for males and 0.5 percent in females, but the water:methanol extracts contained 82.6 percent of the fecal radioactivity in males and 77.9 percent in females. The residue contained 21.3 percent of the fecal radioactivity for males and 23.9 percent in females. The overall recovery was 104 percent for males and 102 percent for females (Table 4).

Figures 2 and 3 show the radioactivity profiles of the acetonitrile extracts of feces for male and female rats, respectively.

In contrast to the low-dose animals, the hexane extracts of feces from Group D rats contained a sizable amount of the administered radioactivity accounting for 2.4 ± 1.02 percent in males and 23.1 ± 1.51 percent in females. The dichloromethane extracts contained further radioactivity, accounting for 3.7 ± 3.16 percent for male rats and 3.8 ± 1.12 percent for female rats.

Captan Science Reviews

Page _____ is not included in this copy.

Pages _14_ through _17_ 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.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action

__X__ 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.

Analysis of the hexane and dichloromethane extracts by HPLC indicated that 90 and 40 percent of the (injected) radioactivity cochromatographed with captan for females and males, respectively. The remainder in males consisted of material that eluted at the solvent front (about 7 percent of the dose) and diffuse radioactivity that was spread over the chromatogram. Figures 4 and 5 show the radicactivity profiles of the acetonitrile extracts for male and female feces, respectively. These chromatograms showed radioactivity eluting at the same retention time as TTC and DMS.

Thin-layer chromatograms were run on samples of acetonitrile extracts from pooled feces sample for both sexes in Groups A and D. The Group A fecal samples showed essentially a dispersed distribution of radioactivity across the chromatogram, so the presence of the specific metabolites could not be confirmed. The Group D fecal samples showed, apart from the broad general distribution of radioactivity, a peak that coeluted with TTC. By TLC, TTC accounted for 32.7 percent of the feces extract in males and 23.8 percent in females. DMS and DMS-O peaks were not sufficiently resolved to be able to specifically identify with confidence.

E. Mass spectrometry of samples taken from the charcoal traps (volatile organics) for Group C animals (1000 mg/kg) 24-36 hours postdosing indicated the presence of dichloromethane in addition to those of residual perfluorocarbons. Dichloromethane was not detected in samples taken from control animals.

13. STUDY AUTHOR'S CONCLUSIONS/QUALITY ASSURANCE MEASURES:

A. The radioanalysis data from Groups A and B were nearly identical, indicating that repeated dosing did not alter captan metabolism. Males excreted 77.4 ± 4.51 percent and 81.9 ± 1.57 percent of the dose in the first 24 hours for

Captan Science Reviews

Page _____ is not included in this copy.

Pages _19_ through _20_ 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.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action

__X__ 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.

Groups A and B, respectively, and females excreted 84.3 ± 8.23 percent and 76.6 ± 3.32 percent for Groups A and B in the first 24 hours, respectively. At sacrifice, the tissues contained 1.73 ± 0.114 percent and 1.63 ± 0.95 percent of the dose for males in Groups A and B, respectively, and 1.75 ± 0.137 percent and 1.16 ± 0.240 percent of the dose for females in Groups A and B, respectively. The major route of elimination was urine, which represented 44.6 ± 5.79 percent and 47.5 ± 3.50 percent of the administered dose in males from Groups A and B, respectively. The other important routes of elimination were feces and expired CO_2. Feces contained 21.5 ± 3.91 percent and 17.6 ± 1.37 percent of the dose in males from Groups A and B, respectively, and 13.6 ± 6.56 percent and 19.5 ± 5.24 percent of the dose in females from Groups A and B, respectively. The expired CO_2 contained 23.5 ± 0.91 percent and 22.0 ± 13.12 percent of the dose in males from Groups A and B, respectively, and 24.5 ± 2.09 percent and 26.3 ± 1.42 percent of the dose in females from Groups A and B, respectively. The tissues that contained the highest concentrations of radioactivity were kidney [0.725 ± 0.049 µg captan equivalents/g (ppm) in Group B males and 0.610 ± 0.31 ppm in Group A males; 0.614 ± 0.08 ppm in Group A females and 0.627 ppm in Group B females] and liver (0.484 ± 0.069 ppm in Group A males and 0.400 ± 0.091 ppm in Group B males; 0.513 ± 0.088 ppm in Group A females and 0.399 ± 0.128 ppm in Group B females). Concentrations in the small intestine with contents were 0.110 ± 0.005 ppm in males and 0.136 ± 0.013 ppm in females from Group A and 0.164 ± 0.051 ppm in males and 0.150 ± 0.028 ppm in females from Group B.

The overall recovery for Group A was 90.5 ± 2.89 percent for males and 90.7 ± 9.27 percent for females and for Group B was 91.8 ± 1.50 percent for males and 91.2 ± 1.15 percent for females.

The results from the high-dose group (D) were different than those of the other two groups. Only 23.7 ± 5.69 percent and 21.0 ± 4.49 percent of the dose was excreted during the first 24 hours in males and females, respectively. The tissues contained 0.90 ± 0.52 percent and 0.86 ± 0.088 percent of the dose at sacrifice in

males and females, respectively. The matrix in which most of the dose was recovered was feces. Male rats excreted 40.1 ± 4.56 percent of the dose, and female rats excreted 32.9 ± 2.76 percent by this route. Other important routes of elimination were expired CO_2, accounting for 14.4 ± 1.38 percent of the dose in males and 14.9 ± 0.72 percent in females, and urinary [^{14}C], accounting for 22.7 ± 5.56 percent of the dose in males and 27.2 ± 1.23 percent in females. In contrast to Groups A and B, where organic volatiles represented less than 1 percent of the dose, in Group D they represented 3.59 ± 0.64 percent of the dose in males and 6.66 ± 0.59 percent in females. The tissues that contained the highest concentrations of captan were liver and kidney. Liver contained 9.90 ± 0.60 ppm in male rats and 11.4 ± 1.73 ppm in female rats, whereas kidney contained 11.2 ± 1.03 ppm in males and 16.2 ± 2.67 ppm in females. The small intestine with contents contained 2.53 ± 0.31 ppm in males and 3.80 ± 0.75 ppm in females. The overall recoveries were 83.3 ± 1.96 percent for males and 83.4 ± 2.84 percent for females. The likely reason for the lower recovery, compared with that of Groups A and B, was the presence of organic volatiles, which were trapped at an unknown efficiency.

Three major urinary metabolites were observed by HPLC as two peaks. They were TTC (22.7 percent of the urinary radioactivity), DMS, and DMS-O, which appeared to coelute under the HPLC conditions employed (65.2 percent combined). Minor metabolites that included radioactivity that eluted at the solvent front (2.6 percent of the urinary radioactivity) and radioactivity that eluted at 18 to 19 minutes (2.3 percent). TLC confirmed the presence of the thiazolidine metabolite and resolved the mixture of sulfonic acids. In male rats, the DMS and DMS-O appeared in approximately equal amounts, whereas in females the former predominated.

In feces at the low dose (Group A), equivocal evidence was obtained for the presence of small amounts of TTC and DMS by HPLC, but this could not be confirmed by TLC. Most of the radioactivity appeared to be either incorporated into natural products or covalently bound to them. This may have occurred by acylation of macromolecules by thiophosgene generated from captan in the gastrointestinal tract.

82

The feces from high-dose animals contained unchanged captan, which represented about 2.4 percent of the fecal radioactivity in feces from male rats and 24.2 percent in feces from female rats. There was evidence of the presence of TTC (10.8 percent of the fecal radioactivity in males and 3.3 percent of the fecal radioactivity in females) in feces from the high-dose animals and equivocal evidence for the presence of DMS and DMS-O. Most of the radioactivity in the feces was either covalently bound or incorporated into natural products. A proposed metabolic pathway is shown in Figure 6.

The charcoal traps from Group C were examined in an attempt to identify the volatile metabolites that appeared in Group D. Neither thermal desorption nor extraction with isooctane or carbon disulfide was successful in releasing the material trapped on the charcoal.

B. A quality assurance statement was signed and dated June 3, 1988.

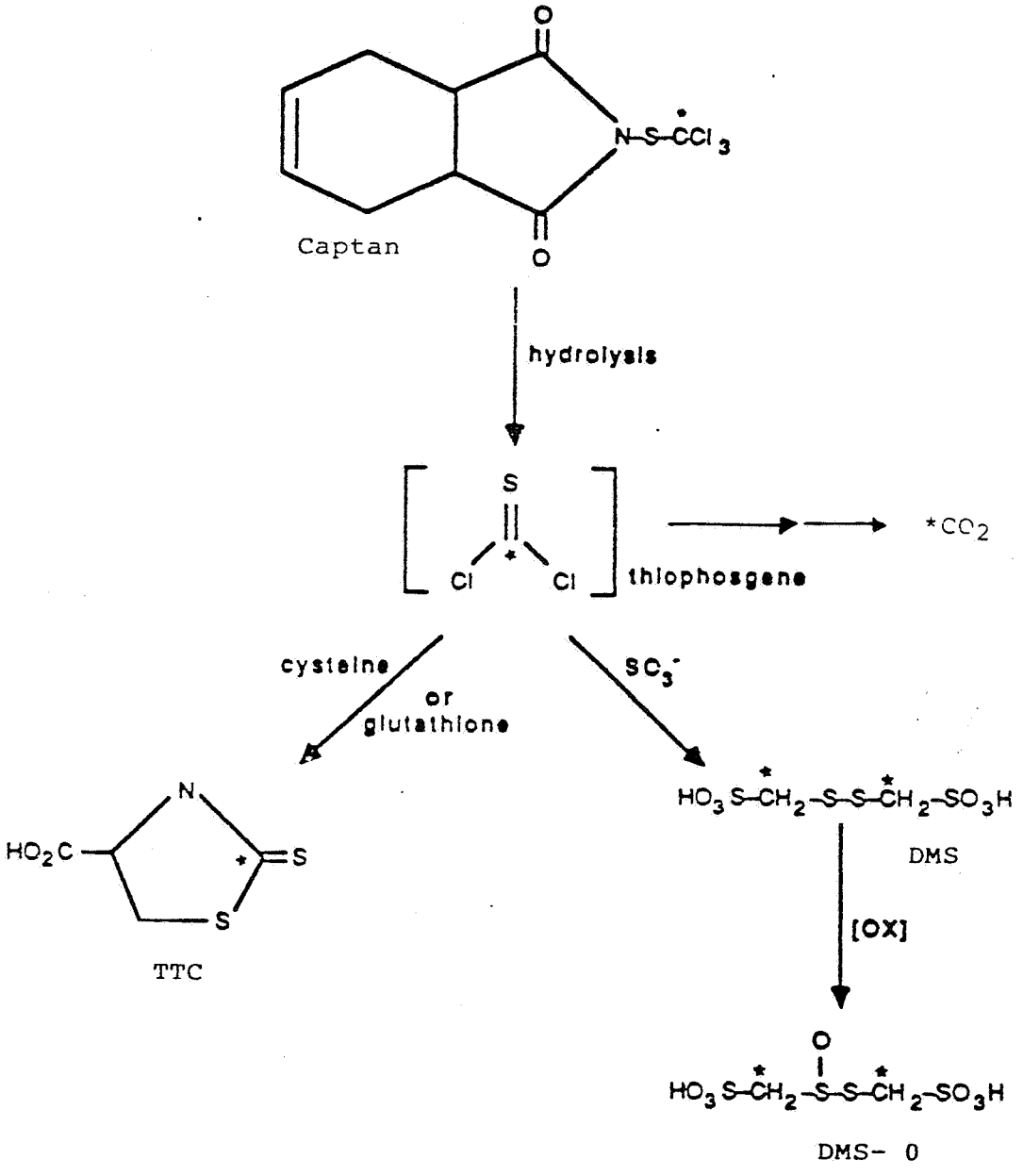
14. REVIEWERS' DISCUSSION AND INTERPRETATION OF STUDY RESULTS:

For the most part, this study was adequately conducted and the author's conclusions are supported by the data presented. The analytical procedures used for feces were apparently inadequate and any conclusions with regards to metabolic identification are speculative. The wide distribution of [^{14}C] may indeed have been due to acylation of macromolecules by [^{14}C]thiophosgene or other intermediate metabolite containing the radiolabelled carbon, since the radiolabelled carbon is in the trichloromethyl moiety.

This study provides information on the metabolism of that moiety only and not the whole molecule. Nonetheless, it would appear that this trichloromethylthio moiety is the toxophoric moiety since the formation of thiophosgene may indeed explain the carcinogenic properties of captan in mice, although no carcinogenic response was observed in rats. The detection of dichloromethane in organic volatiles was not discussed by the author, although it may be indeed an artifact and would not explain the formation of duodenal tumors observed in mice. This study meets EPA guidelines, although it may be necessary to provide information on the metabolism of cyclohexene dicarboximide moiety.

Figure 6

Proposed Pathways for the Metabolism of [trichloromethyl- ^{14}C] Captan in Rats



* denotes position of ^{14}C label

Source: CBI Figure 40, CBI p. 128.

24

Item 15--see footnote 1.

16. CBI APPENDIX: Appendix A, Materials and Met. ods, CBI pp. 132-144.

APPENDIX A

Materials and Methods

Captan Science Reviews

Page _____ is not included in this copy.

Pages _27_ through _39_ 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.

_____ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action

__X__ 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.