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

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MEMORANDUM

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Subject: EPA ID # 081301: Captan - Review of I. In Vitro Dermal Penetration Study, II. Metabolism Study (Pilot), and III. Dermal Penetration Study (Pilot)
Tox. Chem. Number: 159
DP Number: D198354; D198003
MRID Number:430747-01; 430129-02
Submission Number: S455945

From: Paul Chin, Ph.D. Paul Chin 2/23/94
Section 2
Toxicology Branch I
Health Effects Division (H7509C)

To: Linda Propst/Peg Perreault, PM 73
Registration Division (H7505C)

Thru: Joycelyn Stewart, Ph.D. 2/25/94
Section Head
Section 2, Toxicology Branch I
Health Effects Division (H7509C) KB 3/1/94

Registrant: ICI Americas, Inc.

EXECUTIVE SUMMARY:

The Toxicology Branch I reviewed the following three studies:

Study I --In Vitro Dermal Penetration Study (85-2)
Study II --Metabolism Study (85-1), and
Study III--Dermal Penetration Study (85-2).

The summaries of the reviews are shown below. [Detailed reviews are appended to this memorandum.]

Study I. In Vitro Dermal Penetration Study
MRID No.: 430747-01; REPORT TITLE: Captan: In vitro absorption from a 500 g/kg WP formulation through human and rat epidermis

The in vitro dermal absorption rates of captan and its metabolite, tetrahydrophthalimide (THPI), from four different concentrations of a captan 50% WP were determined for human and rat epidermis. For 50% WP captan (200,000 ug/cm^2), the steady state absorption rate of captan by rat epidermis (3.08 ug/cm^2/hr)

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was approximately 10 times higher than for human epidermis (0.27 ug/cm^2/hr). For 1:70 aqueous spray dilution (100 ul/cm^2; 720 ug/cm^2; occluded), the steady state absorption rate for captan by rat epidermis (0.712 ug/cm^2/hr) was approximately 3 times higher than for human epidermis (0.206 ug/cm^2/hr). For 1:70 aqueous spray dilution (10 ul/cm^2; 72 ug/cm^2; unoccluded), the steady state absorption rate for captan by rat epidermis (0.332 ug/cm^2/hr) was more than 30 times higher than for human epidermis (0.009 ug/cm^2/hr). For spray dilution:concentrate (3:1 v/w, 100 ul/cm^2, occluded), the steady state absorption rate for captan by rat epidermis (6.40 ug/cm^2/hr) was approximately 4 times higher than human epidermis (1.56 ug/cm^2/hr).
The steady state absorption rates for THPI through the human and rat skin were as follows: 0.297 and 2.69 ug/cm^2/hr, respectively, for 50% WP captan; 0.074 and 0.15 ug/cm^2/hr, respectively, for 1:70 aqueous spray dilution (720 ug/cm^2); less than limit of detection and 0.117 ug/cm^2/hr, respectively, for 1:70 aqueous spray dilution (72 ug/cm^2); and 1.22 and 2.39 ug/cm^2/hr, respectively, for spray dilution:concentrate (3:1 v/w).

This study is classified as core-Supplementary, because it does not fulfil any Subdivision F guideline for a metabolism or dermal penetration study. Although the study supplies some information to the Agency, it should be noted that:

a) The actual concentration of dosing solution and actual amount applied (ug/cm^2) was not given for spray dilution:concentrate (3:1 v/w, 100 ul/cm^2, occluded). These data are required to evaluate the initial and steady state absorption rates of captan and THPI determined for human and rat skin for this concentration of captan.

b) Individual absorption data are required. The registrant provided only individual and mean absorption data graphically in Figures 1A-8B ("Absorption profiles for captan and THPI"). Therefore, the data are not amenable to statistical evaluation.

c) Use of in vitro dermal absorption data in human skin is not validated for human risk assessment. It only supplies supplementary information.

Study II. Metabolism Study

MRID No: 430129-02; REPORT TITLE:
Captan Metabolism in Humans Yields Two Biomarkers, Tetrahydrophthalimide (THPI) and Thizaolidine-2-thione-4-carboxylic acid (TTCA) in Urine

This is a journal publication.

Captan metabolites, tetrahydrophthalimide (THPI) and

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thiazolidine-2-thione-4-carboxylic acid (TTCA), in urine were measured following a single oral dose of captan at 0.1 or 1 mg/kg in two adult males. Over a 72-hour period, 2.2% of the dose was excreted as THPI after a single oral dose of 1 mg/kg. At single oral dose of 0.1 mg/kg, 1.42% of the dose was excreted as THPI over a 48-hour period. The amounts of TTCA recovered after oral dose of 0.1-1 mg/kg were 4-9% of the administered dose. THPI in the urine samples is stable and the minimum detectable limit (MDL = 5-10 ppb) of THPI is lower than that of TCAA (MDL = 50 ppb). Therefore, the authors concluded that THPI was the preferred biomarker of captan exposure.

This study is classified as Invalid data and does not satisfy the requirement (85-1) for a general metabolism study. The submitted data was not intended to fulfill the guideline requirement (85-1). This study is not applicable for human risk assessment because of inadequate number of subjects used per dose and disparity of two human subjects employed. The registrant is not required to pursue additional studies in this area.

Study III. Dermal Penetration Study

MRID No: 430129-02; REPORT TITLE:
Captan Metabolism in Humans Yields Two Biomarkers, Tetrahydrophthalimide (THPI) and Thizaolidine-2-thione-4-carboxylic acid (TTCA) in Urine

This is a journal publication.

Captan metabolites, tetrahydrophthalimide (THPI) and thiazolidine-2-thione-4-carboxylic acid (TTCA), in urine were measured following a dermal administration of captan (dose unspecified) to hands, forearms, or inguinal region of human males. No urinary THPI was found following a dermal administration of captan (dose unspecified) to hands, forearms, or inguinal region.

This study is classified as Invalid data and does not satisfy the guideline requirement (85-2) for a dermal penetration study. The information provided is not amenable to interpretation since the amount of the chemical administered was not reported. This study is not applicable for human risk assessment because of inadequate number of subjects used per dose and disparity of two human subjects employed. It is not expected that the registrant will pursue additional studies in this area.

REQUESTED ACTION:

The Registration Division requested that the Toxicology Branch review the three studies cited above.

Primary Reviewer: Paul Chin, Ph.D. Paul Chin 2/16/94
Section 2, Tox. Branch 1 (H7509C)
Secondary Reviewer: Joycelyn Stewart, Ph.D., Section Head
Section 2, Tox. Branch 1 (H7509C) 4/23/94

DATA EVALUATION REPORT

STUDY TYPE:	I.	Metabolism (85-1)--Pilot Study
	II.	Dermal Penetration (85-2)--Pilot Study
P. C. No:		081301
MRID No:		430129-02
TEST MATERIAL:		Captan
SYNONYMS:		N-(trichloromethylthio)-4-cyclohexene-1,2-dicarboximide
SPONSOR:		Not provided
TESTING FACILITY:		Western Health and Safety Branch, California EPA, Sacramento, CA
Study (Report) No.:		Published in Drug and Chemical Toxicology, 16 (2), 1993
REPORT TITLE:		Captan Metabolism in Humans Yields Two Biomarkers, Tetrahydrophthalimide (THPI) and Thizaolidine-2-thione-4-carboxylic acid (TTCA) in Urine
AUTHOR(S):		R. J. Krieger and T. Thongsinthusak
REPORT ISSUED:		1993

EXECUTIVE SUMMARY:

This is a journal publication.

I. Metabolism Study

Captan metabolites, tetrahydrophthalimide (THPI) and thiazolidine-2-thione-4-carboxylic acid (TTCA), in urine were measured following a single oral dose of captan at 0.1 or 1 mg/kg in two adult males. Over a 72-hour period, 2.2% of the dose was excreted as THPI after a single oral dose of 1 mg/kg. At single

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oral dose of 0.1 mg/kg, 1.42% of the dose was excreted as THPI over a 48-hour period. The amounts of TTCA recovered after oral dose of 0.1-1 mg/kg were 4-9% of the administered dose. THPI in the urine samples is stable and the minimum detectable limit (MDL = 5-10 ppb) of THPI is lower than that of TCAA (MDL = 50 ppb). Therefore, the authors concluded that THPI was the preferred biomarker of captan exposure.

II. Dermal Penetration Study

Captan metabolites, tetrahydrophthalimide (THPI) and thiazolidine-2-thione-4-carboxylic acid (TTCA), in urine were measured following a dermal administration of captan (dose unspecified) to hands, forearms, or inguinal region of human males. No urinary THPI was found following a dermal administration of captan (dose unspecified) to hands, forearms, or inguinal region.

These studies are classified as Invalid data and do not satisfy the guideline requirements (85-1) for a metabolism study and (85-2) for a dermal penetration study. The submitted data were not intended to fulfill the guideline requirements (85-1) and (85-2). These studies are not applicable for human risk assessment because of inadequate number of subjects used per dose and disparity of two human subjects employed.

The submitted reports are pilot studies in humans to evaluate the influence of route of exposure, dose, and time on THPI and TTCA eliminated following oral or dermal administration of captan.

I. Metabolism Study

A. MATERIALS:

1. Test compounds:
   -Captan of high purity (99.1%, Reference Standard, EPA, Research Triangle Park).
2. Test animals:
   -The subjects were two adult males who weighed 150 kg (331 lb) and 84 kg (185 lb).

B. METHODS:

1. Captan was orally administered as a finely ground solid in gelatin capsules at the rate of 0.1 or 1 mg/kg. Control urine samples were collected 12 hours prior to administration of captan. Urine samples (12 hour intervals) were collected for 4 days.
2. THPI and TTCA in urine samples were analyzed by gas-liquid chromatography and HPLC, respectively.

- A signed and dated Quality Assurance statement was not present.
- A signed and dated GLP statement was not present.

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C. RESULTS:

The metabolism of captan in rats, mice, cattle, goats, and humans is shown in Figure 1. The minimum detectable limits (MDL) for THPI and TTCA were 5-10 ppb and 50 ppb, respectively. Urine samples fortified with THPI (10 and 100 ug) and TTCA (100 ug) resulted in 90-95% and 90% recovery, respectively. The amounts of THPI (expressed as percent urinary captan equivalents) excreted in human urine after a single oral dose of 0.1 or 1 mg/kg are shown in Table 1. "Percent urinary captan is the product of the amount of THPI excreted and the ratio of molecular weight of captan to THPI (301/151) divided by dose."

Over a 72-hour period, 2.2% of the dose was excreted as THPI after a single oral dose of 1 mg/kg. At the lower oral dose (0.1 mg/kg), 1.42% (mean of subjects A and B) of the dose was excreted as THPI over a 48-hour period. The amounts of TTCA recovered after oral dose of 0.1-1 mg/kg were 4-9% of the administered dose (from Table 3 of the study report).

The amounts of THPI and TTCA following an oral dose of 0.1 or 1 mg/kg are shown in Figure 2. The majority of the metabolites were excreted over 24-hour period and slightly more TTCA was present than THPI.

Table 1. The amounts of THPI (expressed as percent urinary captan equivalents) excreted in human urine after a single oral dose of 0.1 or 1 mg/kg.

Dose	Amounts of THPI found as % Captan Equivalents Mean (SD)					
	Time of sampling (Hours)					
	12	24	36	48	72	Total Recovery
1 mg/kg (Subject A)[a]	0.46 (0.06)	0.95 (0.28)	0.33 (0.02)	0.41 (0.32)	0.06 (0.00)	2.21
0.1 mg/kg (Mean of Subjects A and B)	0.67 (ND)[b]	0.46 (ND)	0.20 (ND)	0.09 (ND)	ND	1.42

The subjects A and B were adult males who weighed 150 kg (331 lb) and 84 kg (185 lb), respectively.
a: Mean of three separate experiments conducted using Subject A.
b: ND = not determined

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D. DISCUSSION:

THPI in the urine samples are stable and the minimum detectable limit (MDL = 5-10 ppb) of THPI is lower than that of TCAA (MDL = 50 ppb). Therefore, the authors concluded that THPI was the preferred biomarker of captan exposure.

The report is a pilot study in humans to evaluate the influence of route of exposure, dose, and time on THPI and TTCA eliminated following oral administration of captan. The submitted data was not intended to fulfill the guideline requirement (85-1) for a general metabolism study. Publication do not generally present enough data so that the studies can be independently evaluated. It is not expected that the registrant will pursue additional studies in this area.

II. Dermal Penetration Study

A. MATERIALS:

1. Test compounds:
   -Captan of high purity (99.1%, Reference Standard, EPA, Research Triangle Park).
2. Test animals:
   -The subjects were adult males who weighed 150 kg (331 lb) and 84 kg (185 lb).

B. METHODS:

1. In a preliminary dermal penetration study, captan (150 mg) was dissolved in 10 mL chloroform (15 mg/mL). One mL of solution was transferred via pipette to the palm of the left hand and rubbed over the ventral and dorsal surfaces of the right forearm and hand. "Half of the dose was applied in this manner, and the remainder was applied analogously to the left forearm and hand. Exposed skin was not occluded. The area was washed with soap and hot water after 12 hours. Complete urine samples were collected for five days. A similar procedure was used in a later test when captan solution (mg/kg) was applied to the inguinal region."

   In this study the authors stated that about 15% of the body's surface area was exposed to captan solution (about 40 ug/cm^2 in chloroform) when the hands and forearms were exposed.

2. THPI and TTCA in urine samples were analyzed by gas-liquid chromatography and HPLC, respectively.

- A signed and dated Quality Assurance statement was not present.

- A signed and dated GLP statement was not present.

C. RESULTS:

No urinary THPI was found following a dermal administration of captan (unspecified dose) to hands, forearms, or inguinal region of human males (from Table 3 of the study report).

[NOTE: The method section in this study was not clearly written. Therefore, the actual amount of dosing solution and actual amount of captan applied (ug/cm^2) could not be retrieved from the current dermal penetration study. In this study the authors stated that "about 15% of the body's surface area was exposed to captan solution (about 40 ug/cm^2) when the hands and forearms were exposed."]

D. DISCUSSION:

The report is a pilot study in humans to evaluate the influence of route of exposure, dose, and time on THPI and TTCA eliminated following oral or dermal administration of captan. The submitted data was not intended to fulfill the guideline requirement (85-2) for a dermal penetration study. Publication do not generally present enough data so that the studies can be independently evaluated. It is not expected that the registrant will pursue additional studies in this area.

The study data is inadequately described because it is impossible to tell how much captan was administered to the subjects. Even if that information had been provided the study would still have been inadequate for the purpose of Subdivision F guideline 85-2, because only two subjects were used and the data would not have been applicable to statistical analysis.

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_____Captan review_____

Page _____ is not included in this copy.

Pages __9_ through __10_ 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.

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_____ 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.

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_____ 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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Primary Reviewer: Paul Chin, Ph.D. Paul Chin 2/16/94
Section 2, Tox. Branch 1 (H7509C)
Secondary Reviewer: Joycelyn Stewart, Ph.D., Section Head
Section 2, Tox. Branch 1 (H7509C) 2/23/94

DATA EVALUATION REPORT

STUDY TYPE:	Dermal Penetration (85-2)--In Vitro Study
P. C. No:	081301
MRID No:	430747-01
TEST MATERIAL:	Captan
SYNONYMS:	N-(trichloromethylthio)-4-cyclohexene-1,2-dicarboximide
SPONSOR:	ICI Agrochemicals, Fernhurst, Surrey, UK
TESTING FACILITY:	ICI Central Tox. Lab., Alderley Park, Macclesfield, Cheshire, UK
Study (Report) No.:	JV1321 (CTL/P/2744)
REPORT TITLE:	Captan: In vitro absorption from a 500 g/kg WP formulation through human and rat epidermis
AUTHOR(S):	R. J. Ward, R. C. Scott, and S. J. Hill
REPORT ISSUED:	Oct. 6, 1989

EXECUTIVE SUMMARY:

The in vitro dermal absorption rates of captan and its metabolite, tetrahydrophthalimide (THPI), from four different concentrations of a captan 50% WP were determined for human and rat epidermis. For 50% WP captan (200,000 ug/cm^2), the steady state absorption rate of captan by rat epidermis (3.08 ug/cm^2/hr) was approximately 10 times higher than human epidermis (0.27 ug/cm^2/hr). For 1:70 aqueous spray dilution (100 ul/cm^2; 720 ug/cm^2; occluded), the steady state absorption rate for captan by rat epidermis (0.712 ug/cm^2/hr) was approximately 3 times higher than for human epidermis (0.206 ug/cm^2/hr). For 1:70 aqueous spray dilution (10 ul/cm^2; 72 ug/cm^2; unoccluded), the steady

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state absorption rate for captan by rat epidermis (0.332 ug/cm^2/hr) was more than 30 times higher than for human epidermis (0.009 ug/cm^2/hr). For spray dilution:concentrate (3:1 v/w, 100 ul/cm^2, occluded), the steady state absorption rate for captan by rat epidermis (6.40 ug/cm^2/hr) was approximately 4 times higher than human epidermis (1.56 ug/cm^2/hr).
The steady state absorption rate for THPI through the human and rat skin was as follows: 0.297 and 2.69 ug/cm^2/hr, respectively, for 50% WP captan; 0.074 and 0.15 ug/cm^2/hr, respectively, for 1:70 aqueous spray dilution (720 ug/cm^2); less than limit of detection and 0.117 ug/cm^2/hr, respectively, for 1:70 aqueous spray dilution (72 ug/cm^2); and 1.22 and 2.39 ug/cm^2/hr, respectively, for spray dilution:concentrate (3:1 v/w).

This study is classified as Supplementary data.

The submitted data was not intended to fulfill the guideline requirement (85-2) for a dermal penetration study. This is an in vitro dermal absorption study.

The following deficiencies were noted:

a) The actual concentration of dosing solution and actual amount applied (ug/cm^2) was not given for spray dilution:concentrate (3:1 v/w, 100 ul/cm^2, occluded). These data are required to evaluate the initial and steady state absorption rates of captan and THPI determined for human and rat skin for this concentration of captan.

b) Individual absorption data are required. The registrant provided only individual and mean absorption data graphically in Figures 1A-8B ("Absorption profiles for captan and THPI"). Therefore, the data are not amenable to statistical evaluation.

c) Use of in vitro dermal absorption data in human skin is not validated for human risk assessment. It only supplies supplementary information.

A: MATERIALS:

1. Test compounds:
   -Captan 50 WP formulation (an off-white powder) containing a nominal 500 g captan/kg.
   -Captan technical grade material (a cream colored powder; purity 89.7%); Analytical Certificate Reference No.: 10821-29; Source: ICI Americas Inc.

2. Preparation of Epidermal Membranes:
   -"Human abdominal whole skin (dermis plus epidermis) was obtained post mortem from subjects of various ages. Bias was shown toward female samples, because the more densely haired male samples were less suitable for epidermal separation. Sheets of epidermis were gently

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separated from the dermis following immersion of whole skin in water at 60°C for 40-45 seconds."

-Rat skin: No information was provided.

B. METHODS:

1. Analytical Techniques:
-Captan and tetrahydrophthalimide (THPI), a major captan metabolite, were analyzed by Hewlett-Packard HP5736A gas-liquid chromatography.
-Radioactivity was measured by liquid scintillation counter.

2. Skin Absorption Measurements:
-Glass diffusion cells (see Figure 1), in which the epidermal sheet forms a horizontal membrane separating donor (outer) and receptor chambers, were used for skin absorption rates.
-The integrity of all epidermal membranes was assessed by measurement of their permeability to tritiated water. A measured volume of saline was placed in each receptor chamber. Approximately 1-2 ml of saline containing tritiated water was placed in the donor chamber of each diffusion cell. The appearance of tritium in the receptor solution was followed by taking 25 ul samples between the third and the sixth hour after addition of the donor solution at 0 hours. Radioactivity was assayed and sample counts (cpm/ml) were multiplied by the receptor volume and plotted against time. The permeability coefficient (Kp) for each skin sample was calculated from the linear portion of this plot as follows:

Permeability coefficient (cm/hr) =

$$\frac{\text{slope (cm/hr)}}{\text{mean donor count (cpm/ml) x area of skin (cm}^2\text{)}}$$

Epidermal membranes displaying tritiated water permeability coefficients $>1.5 \times 10^{-3}$ cm/hr (human) or $>2.5 \times 10^{-3}$/hr (rat) were deemed to have been damaged during preparation and rejected. A small amount of saline (0.5 ml) was left in the receptor chamber to maintain the relative humidity overnight and allow the membranes to hydrate naturally.

-Assessment of captan and THPI absorption: The test material was applied to the epidermal membranes as follows: [Area of epidermal membrane = 2.54 cm^2; N = 6]

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Dosing Solution	Amount Applied per cm^2	Amount Applied per cell	Occlusion	Amount applied (ug/cm^2)
Concentrate formulation (50% WP; 500 g/kg)	0.2 g	0.5 g	occluded	200,000
1:70 spray dilution (7.2 g/L)	100 ul	254 ul	occluded	720
1:70 spray dilution (7.2 g/L)[a]	10 ul	25.4 ul	not occluded	72
Spray dilution: concentrate (3:1 v/w) mixture[b]	100 ul	254 ul	occluded	ND[c]

a: The 10 ul/cm^2 unoccluded spray strength dilution application simulates exposure to captan that may be achieved by spray operators in the field.
b: The occluded application of the spray dilution:concentrate mixture represents exposure to an operator involved in both mixing and spraying the formulation.
c: The amount applied can not be calculated due to insufficient information

"A measured volume of 50% v/v ethanol: 0.01M HCl (to prevent captan degradation) was placed into the receptor chamber. At suitable intervals, 0.5 ml samples were taken from the receptor solution to follow the absorption of captan and THPI. Each sample was replaced by an equal volume of fresh 50% v/v ethanol: 0.01M HCl to maintain the volume of receptor solution. Results of the assay of receptor solution samples were expressed as concentrations of captan or THPI. The time-course and rate of absorption, with correction for the volume of sample removed were, determined using the following calculation.

Receptor volume = V;
Sample volume = s;
Concentrations at sampling times (t1, t2, t3 etc) = c1, c2, c3 etc

Thus the amount of penetrant removed from the receptor at t1 = c1 x s etc
The total amount of penetrant having passed through the epidermal membrane at
t1 = c1 x V
t2 = c2 x V + c1 x s

t3 = c3 x V + c1 x s + c2 x s
t4 = c4 x V + c1 x s + c2 x s + c3 x s etc
The amount of penetrant at each time point was divided by the area of epidermal membrane (2.54 cm^2) and the results plotted as amount of penetrant absorbed (ug/cm^2) versus time (hr). The slope of the linear region of this plot gives the rate of absorption of the penetrant per cm^2 of the skin ($ug/cm^2/hr$)."

- A signed and dated Quality Assurance statement was present.
- A signed and dated GLP statement was present.

C. RESULTS:

The in vitro absorption rates ($ug/cm^2/hr$) of captan and its metabolite (THPI) from four different concentrations of a captan 50% WP are shown in Table 1 (human epidermis) and Table 2 (rat epidermis). "Where possible, absorption rates were presented over a period representing a working day (1-10 hours) as well as a steady state absorption rate. Sometimes the two rates overlapped."

a. Neat material (50% WP); 0.2 g/cm^2; occluded application.

Captan absorption
The steady state absorption rate for captan (50% WP) by rat epidermis was approximately 10 times higher than human epidermis. With the human skin an initial absorption rate (1-10 hours) was 0.08 $ug/cm^2/hr$ and steady state absorption rate (24-55 hours) was 0.272 $ug/cm^2/hr$. With the rat skin an initial absorption rate (1-10 hours) was 1.02 $ug/cm^2/hr$ and steady state absorption rate (24-55 hours) was 3.08 $ug/cm^2/hr$.

THPI absorption
The steady state absorption rate for THPI through the human skin was slightly higher than measured for captan. With the human skin an initial absorption rate (1-10 hours) was 0.25 $ug/cm^2/hr$ and steady state absorption rate (6-55 hours) was 0.297 $ug/cm^2/hr$. With the rat skin an initial absorption rate (1-10 hours) was 0.83 $ug/cm^2/hr$ and steady state absorption rate (24-55 hours) was 2.69 $ug/cm^2/hr$.

b. 1:70 Aqueous Spray Dilution; 100 ul/cm^2; occluded application

Captan absorption
The steady state absorption rate for captan (1:70 aqueous spray dilution, occluded) by rat epidermis was approximately 3 times higher than human epidermis.
With the human skin an initial absorption rate (1-10 hours) was 0.147 $ug/cm^2/hr$ and steady state absorption rate (4-55 hours) was 0.206 $ug/cm^2/hr$. With the rat skin an initial absorption rate was reached within 1 hour and steady state absorption rate (1-55

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hours) was 0.712 ug/cm^2/hr.

THPI absorption
The steady state absorption rate for THPI through the human skin was approximately 3 times lower than measured for captan. With the human skin an initial absorption rate (1-10 hours) was 0.034 ug/cm^2/hr and steady state absorption rate (6-55 hours) was 0.074 ug/cm^2/hr. With the rat skin an initial absorption rate (1-10 hours) was 0.18 ug/cm^2/hr and steady state absorption rate (3-31 hours) was 0.15 ug/cm^2/hr.

c. 1:70 Aqueous Spray Dilution; 10 ul/cm^2; unoccluded application

Captan absorption
The steady state absorption rate for captan (1:70 aqueous spray dilution, unoccluded) by rat epidermis was more than 30 times higher than human epidermis. With the human skin an initial absorption rate (1-10 hours) was 0.007 ug/cm^2/hr and steady state absorption rate (24-55 hours) was 0.009 ug/cm^2/hr that is equivalent to less than 1% of applied dose absorbed through human skin during 55 hours of continuous contact. With the rat skin an initial absorption rate was reached within 1 hour and steady state absorption rate (1-31 hours) was 0.332 ug/cm^2/hr that is equivalent to approximately 25% of applied dose absorbed through rat skin during 55 hours of continuous contact.

THPI absorption
THPI absorption through the human skin was less than limit of detection. With the rat skin an initial absorption rate was reached within 1 hour and steady state absorption rate (1-31 hours) was 0.117 ug/cm^2/hr.

d. Spray Dilution:Concentrate (3:1 v/w); 100 ul/cm^2; occluded application

Captan absorption
The steady state absorption rate for captan (spray dilution:concentrate, occluded) by rat epidermis was approximately 4 times higher than human epidermis. With the human skin an initial absorption rate (1-10 hours) was 0.641 ug/cm^2/hr and steady state absorption rate (10-55 hours) was 1.56 ug/cm^2/hr. With the rat skin an initial absorption rate was reached within 1 hour and steady state absorption rate (1-55 hours) was 6.40 ug/cm^2/hr.

THPI absorption
The steady state absorption rate for THPI through the human skin was slightly lower than measured for captan. The maximum rate of THPI occurred during the 4-10 and 1-10 hours for human and rat skin, respectively. With the human skin an initial absorption rate (1-10 hours) was 0.963 ug/cm^2/hr and steady state absorption rate (4-10 hours) was 1.22 ug/cm^2/hr. With the rat skin an

initial absorption rate was reached within 1 hour and steady state absorption rate (1-10 hours) was 2.39 ug/cm^2/hr.

D. DISCUSSION:

Based on the various applications made, the steady state absorption rates of captan by rat epidermis varied between 3-fold (occluded application of 720 ug/cm^2) and more than 30-fold (unoccluded application of 72 ug/cm^2) when compared to human epidermis. However, these dermal absorption values should be used with extreme caution because these values may be underestimated due to the poor solubility of captan in ethanol:water (1:1) solution in receptor chamber.

For spray dilution:concentrate (3:1 v/w, 100 ul/cm^2, occluded), the actual concentration of dosing solution and actual amount applied (ug/cm^2) was not given in the report. Therefore, the initial and steady state absorption rates of captan and THPI by human and rat skin for this concentration of captan are meaningless.

THPI was detected in receptor fluid samples, however, the appearance of THPI in the receptor was due to the presence of THPI as an impurity in the captan formulation (as much as [redacted] w/w) rather than due to degradation of captan during the experiment.

IMPURITY

[redacted] INFORMATION IS NOT INCLUDED

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Table 1. In vitro absorption of captan by human and rat epidermis. Values are means of 6 experiments.

Dosing Solution	Amount Applied (ug/cm^2)	Mean absorption rate $ug/cm^2/hr$ (SEM)			
		Time period (hrs)	Human	Time period (hrs)	Rat
Concentrate formulation (50% WP; 500 g/kg); occluded	200,000	1-10 24-55	0.080 (0.045) 0.272 (0.108)	1-10 24-55	1.02 (0.632) 3.08 (1.09)
1:70 spray dilution (7.2 g/L); occluded	720	1-10 4-55	0.147 (0.030) 0.206 (0.037)	1-55	0.712 (0.124)
1:70 spray dilution (7.2 g/L); not occluded	72	1-10 24-55	0.007 (0.002) 0.009 (0.003)	1-31[1]	0.332 (0.079)
Spray dilution: concentrate (3:1 v/w) mixture; occluded	can not be estimated due to inadequate information in the report	1-10 10-55	0.641 (0.103) 1.56 (0.131)	1-55	6.40 (0.428)

[1] Maximum rate

Table 2. In vitro absorption of THPI by human and rat epidermis. Values are means of 6 experiments.

Dosing Solution	Amount Applied (ug/cm^2)	Mean absorption rate $ug/cm^2/hr$ (SEM)			
		Time period (hrs)	Human	Time period (hrs)	Rat
Concentrate formulation (50% WP; 500 g/kg); occluded	200,000	1-10 6-55	0.250 (0.090) 0.297 (0.085)	1-10 24-55	0.830 (0.345) 2.69 (0.822)
1:70 spray dilution (7.2 g/L); occluded	720	1-10 6-55	0.034 (0.011) 0.074 (0.012)	1-10[1] 3-31[1]	0.178 (0.028) 0.152 (0.028)
1:70 spray dilution (7.2 g/L); not occluded	72		Not determined	1-31[1]	0.117 (0.029)
Spray dilution: concentrate (3:1 v/w) mixture; occluded	can not be estimated due to inadequate information in the report	1-10[1] 4-10[1]	0.963 (0.205) 1.22 (0.268)	1-10[1]	2.39 (0.307)

[1] Maximum rate

_____Captan review_____

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