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

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

FEB 23 1990

C07778

MEMORANDUM

SUBJECT: EPA ID No. 10182-181 Butylate - Toxicology Data Submitted in Response to the Registration Standard (MRID No. 41037301)

TOX Chem No.: 434A
TB Project No.: 9-1292
RD Record No.: 243530

FROM: Irving Mauer, Ph.D./Paul Chin, Ph.D.
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (H7509C)

TO: Joanne I. Miller, Acting PM 23
Fungicide-Herbicide Branch
Registration Division (H7505C)

THRU: Karl Baetcke, Ph.D., Chief
Toxicology Branch I - Insecticide, Rodenticide Support
Health Effects Division (H7509C)

Registrant: ICI Americas, Wilmington, DE

Conclusions

The data requirement for metabolism (85-1) for SUTAN (butylate) has been satisfied when the following 3 studies are considered together (Comments 1, 2, and 3). These metabolism studies showed that SUTAN is rapidly absorbed, extensively metabolized and rapidly excreted during the 5 days following acute or repeated oral administration of (isobutyl-1-^{14}C) SUTAN. There is no indication of bioaccumulation of SUTAN in any tissue or organ. The major routes of biotransformation of SUTAN are sulfoxidation followed by glutathione conjugation, and hydrolysis or alpha-oxidation of the S-ethyl group followed by hydrolysis.

Request

Review and evaluate the following rat metabolism study submitted in response to a data gap identified in the Butylate Registration Standard:

> SUTAN Metabolism Study in Rats, performed at the CIBA-GEIGY Environmental Health Center, Farmington, CT, Study No. T-12977, Final Report dated February 14, 1989 (EPA MRID No. 41037301).

Comment 1:

MRID No. 41037301 (Study No. T-12977, DER is attached) was ACCEPTABLE. However, this study alone does not fully satisfy the toxicology Test Guidelines data requirement for metabolism (85-1), because rat metabolism data from only a single (low) dose (20 mg/kg) and repeated low doses (20 mg/kg) were fully generated. [See detailed data review attached to this memorandum.] However, when data from two other studies (MRID Nos. 00043680 [see Comment 2, below] and 00129397 [see Comment 3, below], each of which also only partially satisfied the metabolism data requirements) are considered together with the results of this study, the toxicology requirement for adequate metabolism data in the rat is fully satisfied.

This study (T-12977) showed that after acute or repeat oral administration of 20 mg/kg (isobutyl-1-^{14}C)-SUTAN, test compound was rapidly absorbed, extensively metabolized and rapidly excreted. Over a 3-day period, most (88%) of the administered dose was recovered with 80 percent in the urine, 4 percent in feces, and 4 percent as CO_2 in the expired air. There was no indication of bioaccumulation in any tissue or organ. SUTAN was extensively metabolized, and none of the parent compound was found in urine. The major routes of biotransformation of SUTAN are sulfoxidation followed by glutathione conjugation, and hydrolysis or alpha-oxidation of the S-ethyl group followed by hydrolysis. Among a total of 29 metabolites appearing in the urine, 18 metabolites were identified. The major metabolite was diisobutylamine (36 to 40% of the administered dose, 45 to 50% of urinary radioactivity). Other metabolites identified were hydroxylated diisobutylamine, hydroxylated and unhydroxylated mercapturates, and the S-glucuronide conjugate of diisobutylthiocarbamic acid representing 3 to 10, 1 to 5, and 5 to 8 percent of the administered dosed, respectively.

Comment 2:

MRID No. 00043680 (Study Nos. MRC-79-12 and MRC-B-97, DER is attached) was considered ACCEPTABLE but this study alone does not fulfill the guideline requirement because only a single high-dose level was employed for the excretion and tissue distribution study of SUTAN in rats.

SUTAN was rapidly eliminated from the animals and there was no indication of bioaccumulation in any tissues or organs 3 days after a single oral administration of 100 mg/kg ^{14}C-SUTAN. Over a 3-day period, greater than 100 percent of the test compound administered was excreted from the animals. The radioactivity recovered in urine, feces and CO_2 in exhaled air was 94, 4, and 2 percent of the administered dose, respectively. The amount of SUTAN equivalent remaining in the animals was less than 1 percent of the administered dose.

Comment 3:

MRID No. 00129397 (Study Nos. PMS-108 and MRC 83-06, DER is attached) was judged CORE-SUPPLEMENTARY because only a single high-dose level was employed and solely the excretion and no tissue distribution of SUTAN in rats was measured.

The excretion of SUTAN was studied in rats following an single oral administration of 100 mg/kg (isobutyl-^{14}C)-SUTAN. Over a 2-day period, all (101.7%) of the administrated dose was recovered with 88.4 percent in the urine, 10.5 percent in feces, and 6.8 percent as volatile amines in the air trap (HCl). The radioactivity in the respiratory CO_2 was not determined.

Background

Additionally, the Toxicology Branch (TB) reviewed a corn metabolism study (EPA memorandum by C. D. Sandusky, dated March 12, 1985; located in the Butylate Registration Standard file) because of the presence of two metabolites not found in animal studies. We concluded that these two plant metabolites (XII and XIII, see Table 1 below for chemical names and structures) could be of potential toxicological concern; however, the established tolerance for butylate is 0.1 ppm (level of detection) and these metabolites are not likely to "present an undue hazard."

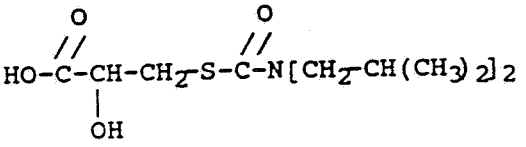
The Dietary Exposure Branch (DEB) concurred with the conclusion of TB; however, DEB stated that if additional registrations on food or feed crops other than corn are

3

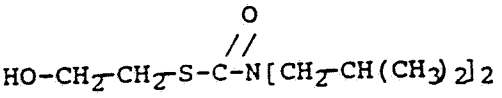
sought, or a tolerance increase is proposed, additional animal metabolism data will be required (EPA memorandum, Trichilo (DEB) to Engler and Kent, October 25, 1988; located in the Residue Chemistry Chapter for the Butylate Second Round Review Registration Standard).

Table 1. Chemical Names and Structures of Plant Metabolites XII and XIII (Source: MRID No. 00129398)

Plant Metabolite	Chemical Name and Structure
XII	S-(2-hydroxy-2-carboxyethyl)-N,N-diisobutylthiocarbamate



XIII	S-(2-hydroxyethyl)-N,N-diisobutylthiocarbamate



Attachment (DERs)

4

007778

Reviewed by : Irving Mauer, Ph.D. and Paul Chin, Ph.D. Paul Chin 1/29/90
Toxicology Branch I (H7509C)
Secondary Reviewer: Karl P. Baetcke, Ph.D., Chief
Toxicology Branch I (H7509C) 2/6/90

DATA EVALUATION RECORD

007778

I. SUMMARY

MRID No.: 41037301
ID No.: 10182-181
RD Record: 243530
Shaghnessy No.: 041405
Tox Chem No.: 434A
TB Project: 9-1292

Study Type: (85-1) Metabolism - Rat

Chemical: Butylate (S-ethyl-N,N-diisobutylthiocarbamate)

Synonyms: SUTAN®, R-1910

Sponsor: ICI Americas, Wilmington, DE

Testing Facility: CIBA-GEIGY Environmental Health Center (EHC), Farmington, CT

Title of Report: SUTAN Metabolism Study in Rats.

Authors: R.C. Peffer and D.D. Campbell

Study No.: T-12977

Date of Issue: Final Report issued February 14, 1989
(Study completed August 15, 1988)

TB Conclusions:

This study showed that after acute or repeat oral administration of 20 mg/kg (isobutyl-1-^{14}C)-SUTAN, test compound was rapidly absorbed, extensively metabolized and rapidly excreted. Over a 3-day period, most (88%) of the administered dose was recovered with 80 percent in the urine, 4 percent in feces, and 4 percent as CO_2 in the expired air. There was no indication of bioaccumulation in any tissue or organ. SUTAN was extensively metabolized, and none of the parent compound was found in urine. The major routes of biotransformation of SUTAN are sulfoxidation followed by glutathione conjugation, and hydrolysis or alpha-oxidation of the S-ethyl group followed by hydrolysis. Among a total of 29 metabolites appearing in the urine, 18 metabolites were identified. The major metabolite was

5

diisobutylamine (36 to 40% of the administered dose, 45 to 50% of urinary radioactivity). Other principal metabolites identified were hydroxylated diisobutylamine, hydroxylated and unhydroxylated mercapturates, and the S-glucuronide conjugate of diisobutylthiocarbamic acid representing 3 to 10, 1 to 5, and 5 to 8 percent of the administered dosed, respectively.

Classification (Core-Grade):

ACCEPTABLE. The requirement for metabolism data for SUTAN in the rat is satisfied when considered together with two other studies [MRID No. 00043680 (Study Nos. MRC-79-12 and MRC-B-97) and MRID No. 00129397 (Study Nos. PMS-108 and MRC 83-06)]. This study by itself does not satisfy the toxicology data requirement for metabolism.

II. DETAILED REVIEW

A. Test Materials

	SUTAN (Unlabeled Technical)	(isobutyl-1-^{14}C) SUTAN
Description	Colorless liquid	Colorless liquid
Batch (Lot)	8993-45-1	WIZ-003
Purity (%)	99.4	99.6
Solvent	Corn oil	1,2-Propanediol: Ethanol mixture
Source	de Guigne Technical Center, Stauffer Chemical, Richmond, CA	Wizard Labs, W. Sacramento, CA

B. Test Organism - Rodent

Species: Rat
Strain:Sprague-Dawley derived [=Crl:CD\ (SD)BRVAF/Plus]
Age: 7-9 Weeks
Weights - Males: 241 to 273 g
Females: 156 to 185 g
Source: Charles River, Kingston, NY

C. Study Design (Protocol) - This study was designed to determine the absorption, distribution, metabolism and elimination of SUTAN when administered by oral gavage to rats after a single or repeat low-dose schedule.

Test Group	Dose Level (mg/kg)	Route of Administration	Number of Animals M	F	Air Collection
I	20	Repeated oral	5	5	10% KOH traps
II	20	Single oral	5	5	10% KOH traps
III	400	Single oral	0	2	None

Signed statements of No Confidentiality Claim, compliance with EPA GLPs, and Quality Assurance measures were provided.

D. Procedures/Methods of Analysis - Following quarantine (7 days) and acclimation to individual glass metabolism cages (4 days +), five males and five females were administered radiolabeled SUTAN (specific activity = 23.8 mCi/mmol) as a single oral dose of 20 mg/kg (Group I), while a second group of five animals/sex (Group II) was pretreated orally with 20 mg/kg/day unlabeled SUTAN for 14 days prior to the administration of the radioactive test material. In order to collect larger amounts of excretory metabolites for trace metabolite analysis, an additional two females (Group III) were dosed acutely with 400 mg/kg radiolabeled SUTAN.

Urine and feces were collected from all groups at 6, 12, 24, 36, 48, and 72 hours after dosing with radiolabeled SUTAN, and air, trapped in 10% KOH, was collected at 6, 12, 24, and 30 hours postdose. At 72 hours, all animals were anesthetized, exsanguinated by cardiac puncture until death, necropsied, and the following organs/tissues were weighed: Liver, kidneys, gonads, brain, heart, spleen, lungs, stomach (and contents), and large/small intestine (and contents); tissue samples of mesenteric fat, skeletal muscle and skin; the remaining carcass.

Radioactive content of study organ, tissue, and remaining carcass samples was measured by liquid scintillation procedures appropriate to the specific samples.

Urinary metabolites were isolated, purified, and identified by positive and negative ion thermospray HPLC/MS, positive ion electron impact GC/MS or chemical ionization GC/MS, using acknowledged brand-name instrumentation and by referenced techniques. Metabolite quantitation was assured by using

1

derivatized samples scraped from TLC plates. Because of the low amounts of radioactivity excreted in feces (< 5%), fecal metabolites were not examined.
The following raw data were analyzed statistically:

1. Total radioactivity in tissues, excreta, air-trap material, and cage washings was determined from the total weight of each processed sample and net dpm/g in aliquots, which furnished percent recoveries. Residual radioactivity in tissues(ng SUTAN equivalent/g tissue) was determined by dividing tissue concentration (dpm/g) by specific activity of administered dose (dpm/ng SUTAN). Both recovery and tissue radioactivity data were analyzed by Duncan's multiple range test using the current version of a commercial statistics package (NWA Statpak, Northwest Analytical, Inc.).

2. Percent urinary radioactivity of each metabolite was calculated from mean percent total radioactivity compared to the contents in pH 10 ether, pH 1 ether, and aqueous fractions.

E. Results

SUTAN was rapidly absorbed, extensively metabolized, and excreted during the 3 days following oral administration of what the authors considered a "low" dose (20 mg/kg) of isobutyl-1-^{14}C-SUTAN (Report Tables 3 to 6 and Figure 3).

[Individual animal data were collected as Appendices I through IV from which summary tabulations and figures were constructed. Selected summary data from these compilations are appended to this DER as ATTACHMENT I.]

1. Excretion

The major route of excretion for SUTAN was via the urine in both sexes. Recovery of urinary radioactivity over 72 hours was 80.9 percent of the administered dose in females and 78.7 percent in males (Report Tables 3 to 5 and Figure 3).

Fecal radioactivity was minimal in both sexes (5.7% of administered dose in males, which was significantly more than the 1.9% in females, $p < 0.05$)), while $^{14}CO_2$ in expired air yielded 4.2 percent for males and 2.8 percent for females (also $p < 0.05$). Residues in cage washes accounted for < 1 percent of administered dose in all test groups.

Recovery of radioactivity in urine was also

significantly higher ($p < 0.05$) in repeat-dose females (82.5%) than in single-dose females (79.37%); however, no significant difference was found between repeat-dose (79.1%) and single dose (78.4%) males.

2.Tissue Distribution

The amount of residual radioactivity in tissues was minimal after 72 hours (< 1% of the administered dose), indicating that the potential for bioaccumulation is minimal. Small but consistent sex differences were found, however, concentrations being higher principally in male livers and small intestine samples after single or repeat doses (Report Tables 6 and 9).

3.Total Recovery

Total recovery from all locations averaged 89.8 percent in males and 86.3 percent in females, with most of the test compound being excreted in urine (see ATTACHMENT I to this DER).

4.Metabolites

The major routes of biotransformation of SUTAN are sulfoxidation followed by glutathione conjugation, and hydrolysis, or alpha-oxidation of the S-ethyl group followed by hydrolysis (Report Figure 39a). Other minor metabolic pathways for SUTAN were N-alkyl hydroxylation, N-dealkylation, and formation of cyclized rearrangement products and beta-oxidation of the S-ethyl group (Report Figures 39b and 39c).

No parent compound (unmetabolized SUTAN) was detected in urine. Among a total of 29 metabolites appearing in the urine (each > 0.2% of the urinary radioactivity), 18 metabolites which represent most (90%) of the urinary radioactiovity (ca. 72% of administered dose) were identified (Report Tables 13 and 15).

The major metabolite identified was diisobutylamine (45 to 50% of urinary radioactivity or 36 to 40% of administered dose), with lesser amounts of primary and tertiary hydroxylated congeners (3 to 10% of the dose), plus hydroxylated and unhydroxylated mercapturates (1 to 4%) and the S-glucuronide conjugate of diisobutyl-thiocarbamic acid (5 to 8%) (Report Figure 39a).

F. TB Conclusions - ACCEPTABLE.

This study appears to have been conducted in an adequate manner to generate valid results related to the absorption, tissue distribution, elimination, and biotransformation of SUTAN in rats after single or repeat oral doses of 20 mg/kg. All but a small amount of radioactivity was accounted for (total recovery = ca. 90%), and the data disclosed extensive metabolism of the single administered low dose (20 mg/kg), with rapid excretion (primarily urinary), and only minute tissue accumulation. Among a total of 29 metabolites appearing in the urine (ca. 90% of urinary radioactivity, representing 72% of administered dose), 18 metabolites were identified, and plausible schemes for the metabolism of the test substance proposed.

This study alone does not fully satisfy the toxicology Test Guidelines data requirement for metabolism (85-1), because rat metabolism data from only a single (low) dose (20 mg/kg) and repeated low doses (20 mg/kg) were fully generated. However, when data from two other studies (MRID Nos. 00043680 [see Comment 1, below] and 00129397 [see Comment 2, below], each of which also only partially satisfied the metabolism data requirements) are considered together with the results of this study, the toxicology requirement for metabolism data in the rat is fully satisfied. Hence, the data gap enunciated in the Registration standard for a general metabolism study of SUTAN in the rat is fulfilled.

Comment 1:

MRID No. 00043680 (Study Nos. MRC-79-12 and MRC-B-97, DER is attached) was considered ACCEPTABLE but this study alone does not fulfill the guideline requirement because only a single high-dose level of 100 mg/kg was employed for the excretion and tissue distribution study of SUTAN in rats.

SUTAN was rapidly eliminated from the animals and there was no indication of bioaccumulation in any tissues or organs 3 days after a single oral administration of 100 mg/kg ^{14}C-SUTAN. Over a 3-day period, greater than 100 percent of the test compound administered was excreted from the animals. The radioactivity recovered in urine, feces, and CO_2 in exhaled air was 94, 4 and 2 percent of the administered dose, respectively. The amount of SUTAN equivalent remaining in the animals was less than 1 percent of the administered dose.

Comment 2:

MRID No. 00129397 (Study Nos. PMS-108 and MRC 83-06, DER is attached) was judged CORE-SUPPLEMENTARY because only a single high-dose was employed and solely for the excretion and no tissue distribution of SUTAN in rats was measured.

The excretion of SUTAN was studied in rats following an single oral administration of 100 mg/kg (isobutyl-^{14}C)-Sutan. Over a 2-day period, all (101.7%) of the administrated dose was recovered with 88.4 percent in the urine, 10.5 percent in feces, and 6.8 percent as volatile amines in the air trap (HCl). The radioactivity in the respiratory CO_2 was not determined.

Attachment

ATTACHMENT I

SUMMARY TABLES
FIGURES

17

Butylate toxicology review

Page _____ is not included in this copy.

Pages 13 through 25 are not included in this copy.

The material not included contains the following type of information:

___ Identity of product inert ingredients

___ Identity of product 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.

Paul Chin 1/29/90 007778

Primary Reviewer: Paul Chin, Ph.D.
Section 2, Toxicology Branch I (IRS) (H7509C)
Secondary Reviewer: Marion Copley, D.V.M., D.A.B.T. MCopley 1/29/90
Section 2, Toxicology Branch I (IRS) (H7509C)

DATA EVALUATION REPORT 007778

STUDY TYPE: Metabolism - Rat (85-1)

Tox Chem No: 434A
MRID No: 0043680
TB Project No: 9-1292

TEST MATERIA: Butylate (S-ethyl-N,N-diisobutylthiocarbamate)

SYNONYMS: SUTAN ®, R-1910

SPONSOR: Stauffer Chemical Company

TESTING FACILITY: Mountain View Research Center,
Mountain View, CA 94042

STUDY NO.: MRC-79-12, MRC-B-97

REPORT TITLE: Metabolism of [Isobutyl-^{14}C] SUTAN in the Rat: Balance and Tissue Residue Study.

AUTHORS: D.B. Thomas, J.B. Miaullis, A.R. Vispetto, and J. Osuna

REPORT ISSUED: August 1979

CONCLUSIONS:

SUTAN was rapidly eliminated from the animals and there was no indication of bioaccumulation in any tissues or organs 3 days after a single oral administration of 100 mg/kg ^{14}C-SUTAN. Over a 3-day period, greater than 100 percent of the test compound administered was excreted from the animals. The radioactivity recovered in urine, feces, and CO_2 in exhaled air was 94, 4 and 2 percent of the administered dose, respectively. The amount of SUTAN equivalent remaining in the animals was less than 1 percent of the administered dose.

CLASSIFICATION (Core-Grade): Acceptable

The requirement for metabolism data for SUTAN in the rat is satisfied when considered together with two other metabolism studies [MRID Nos. 41037301 (Study No. T-12977, see Comment 1, below) and 00129397 (Study Nos. PMS-108 and MRC 83-06, see Comment 2, below)], each of which also partially satisfied the metabolism data requirements]. This study by itself does not satisfy the toxicology data requirement for metabolism.

Comment 1

MRID No. 41037301 (Study No. T-12977). Peffer, R.C.; Campbell, D.D.
SUTAN Metabolism Study in Rats, February 14, 1989, Submitted by ICI Americas, Wilmington, DE.

This study was considered ACCEPTABLE. However, this study alone does not fulfill the guideline requirement because this metabolism study was limited to adsorption, tissue distribution, elimination, and biotransformation of SUTAN in rats after a single oral dose (20 mg/kg) or repeated oral doses (20 mg/kg). In this study, a high dose level of SUTAN was not employed.

This study showed that after acute or repeat oral administration of 20 mg/kg (isobutyl-1-^{14}C)-SUTAN, test compound was rapidly absorbed, extensively metabolized and rapidly excreted. Over a 3-day period, most (88%) of the administered dose was recovered with 80 percent in the urine, 4 percent in feces, and 4 percent as CO_2 in the expired air. There was no indication of bioaccumulation in any tissue or organ. SUTAN was extensively metabolized, and none of the parent compound was found in urine. The major routes of biotransformation of SUTAN are sulfoxidation followed by glutathione conjugation, and hydrolysis or alpha-oxidation of the S-ethyl group followed by hydrolysis. Among a total of 29 metabolites appearing in the urine, 18 metabolites were identified. The major metabolite was diisobutylamine (36 to 40% of the administered dose, 45 to 50% of urinary radioactivity). Other principal metabolites identified were hydroxylated diisobutylamine, hydroxylated and unhydroxylated mercapturates, and the S-glucuronide conjugate of diisobutylthiocarbamic acid representing 3 to 10, 1 to 5, and 5 to 8 percent of the administered dosed, respectively.

Comment 2

MRID No. 00129397 (Study Nos. PMS-108 and MRC 83-06, HED Document No. 005124). Ross, J.H.; Bova-Thomas, D.L.; Osuna,

21

J.J.; Bowler, D.J. Metabolism of [1-Isobutyl-^{14}C] SUTAN in the rat: Urinary Metabolite Identification. PMS-108, MRC 83-06, June 1983, submitted by Stauffer Chemical Company.

This study was considered CORE-SUPPLEMENTARY because only a single high dose level was employed and solely the excretion and no tissue distribution of SUTAN in rats was measured.

The excretion of SUTAN was studied in rats following single oral administration of 100 mg/kg (isobutyl-^{14}C)-SUTAN. Over a 2-day period, all (101.7%) of the administrated dose was recovered, with 88.4 percent in the urine, 10.5 percent in feces, and 6.8 percent as volatile amines in the air trap (HCl). The radioactivity in the respiratory CO_2 was not determined.

TEST MATERIALS:

	SUTAN (Unlabeled technical)	(Isobutyl-1-^{14}C)-SUTAN
Purity %	97.9	> 96
Solvent/diluent	1,2-propanediol	1,2-propanediol
Source	Not reported	De Guigne Technical Center, Stauffer Chemical Company, Richmond, CA

COMPOSITION OF DOSING SOLUTION:

^{14}C-SUTAN	0.0025 g
Unlabeled SUTAN	0.1298 g
1,2-Propanediol	1.7571 g
Total	1.8894 g

TEST ORGANISM - Rodent

Species:	Rat
Strain:	Sprague-Dawley derived
Age:	Unspecified
Weights:	Males - 215, 221 g Females - 311, 314 g
Source:	Simonsen Laboratories Gilroy, CA

STUDY DESIGN:

This study was designed to determine the excretion and tissue distribution of SUTAN when administered by oral gavage to rats at 100 mg/kg.

PROCEDURES/METHODS OF ANALYSIS:

After 12 hours of fasting, two males and two females were administered ^{14}C-SUTAN (total dpm/rat = 4.76 to 4.85 x 10^7) as a single oral dose ranging from 100 to 118 mg/kg.

Urine, feces, and air, trapped in 10% KOH, were collected from both groups at 12, 24, 48, and 72 hours after dosing. In order to reduce volatility, urine and feces were collected in ice water baths throughout the study. At 72 hours after dosing, all animals were sacrificed by cervical dislocation.

25

Blood was removed via heart puncture with a heparinized syringe. The following organs/tissues were weighed: liver, kidneys, gonads, brain, heart, spleen, lungs, stomach (with contents) and large/small intestine (with contents), fat, bone, muscle, and remaining carcass. Radioactive content of study organs, tissues, and remaining carcass samples was measured by liquid scintillation procedures appropriate to the specific samples.

RESULTS:

SUTAN was rapidly eliminated from the animals and there was no indication of bioaccumulation in any tissues or organs 3 days after the single oral administration of 100 mg/kg ^{14}C-SUTAN.

1. Excretion - Table 1 shows the distribution of radioactivity in urine, feces, and CO_2 in exhaled air from rats 72 hours after dosing with ^{14}C-SUTAN. The average total recovery of SUTAN was greater than 100 percent of the administered dose. [Individual animal data are shown in Report Table II, see Attachment I to this DER]

   The major route of excretion for SUTAN was via the urine in both sexes. The average total recovery of radioactivity in the urine, feces, and CO_2 in exhaled air was 94, 4, and 2 percent of the administered dose, respectively. Although total recovery of radioactivity did not vary between the sexes (87 to 91% and 87 to 95% of the dose in males and females, respectively), rates of excretion of radioactivity in the urine 12 hours after the administration of SUTAN was somewhat different between the sexes (58 to 64% and 46 to 50% of the dose in males and females, respectively). However, these differences were not analyzed for statistical significance because only four animals (two males and two females) were used.

30

Table 1. Excretion of Radioactivity in the Urine, Feces, and Expired CO_2 as % of Dose From Rats Following a Single Oral Administration of ^{14}C-SUTAN at Approximately 100 mg/kg

	Recovery, as % of Dose[a]		
	Hours After Administration		
	24	48	72
Urine[b]	88.1	89.4	93.8
Feces	3.6	4.0	4.0
CO_2	1.9	2.0	2.0
Total	93.6	95.4	99.8

[a]Values are cumulative average of two male and two female rats. Data excerpted from Table II from the report.
[b]Includes cage washes.

2. Tissue Distribution - The amount of residual radioactivity in organs/tissues from rats was less than 1 percent of the administered dose 72 hours after administration of ^{14}C-SUTAN, indicating that the potential for bioaccumulation of SUTAN is minimal (See Attachment I, Report Table 2). Radioactivity reported for each specimen was expressed in ppm SUTAN equivalents per gram weight of specimen. The majority of the organs/tissues from both sexes contained less than 1 ppm SUTAN equivalents. Organs/tissues that contained greater than 1 ppm SUTAN equivalents were the liver (1.72 ppm, 0.08% of the dose), the distal portion of the small intestine (1.48 ppm, 0.03% of the dose) and the blood (1.28 ppm, % of the dose unspecified). Highest amounts of radioactivity were observed in carcasses (0.23% of the dose), the liver (0.08%), the skin (0.08%), and the distal portion of the small intestine (0.03%).

DEFICIENCIES:

Usefulness of the information obtained from this study is limited due to the following deficiencies:

1. It was not specified whether the rats were acclimated before the administration of the test substance.

31

2. Sample size in this study was extremely small (only two male and two female rats were used). Therefore, the findings reported in this study cannot be supported statistically.
3. Only one high dose (100 mg/kg) was used.
4. Type and quantities of trace impurities of labeled SUTAN were not reported.

TB CONCLUSIONS - ACCEPTABLE

The requirement for metabolism data for SUTAN in the rat is satisfied when considered together with two other metabolism studies [MRID Nos. 41037301 (Study No. T-12977, see Comment 1, page 2 of this DER) and 00129397 (Study Nos. PMS-108 and MRC 83-06, see Comment 2, page 2 of this DER)], each of which also partially satisfied the metabolism data requirements. This study by itself does not satisfy the toxicology data requirement for metabolism.

SUTAN was rapidly eliminated from the animals and there was no indication of bioaccumulation in any tissues or organs 3 days after a single oral administration of 100 mg/kg ^{14}C-SUTAN. Over a 3-day period, greater than 100 percent of the test compound administered was excreted from the animals. The radioactivity recovered in urine, feces, and CO_2 in exhaled air was 94, 4 and 2 percent of the administered dose, respectively. The amount of SUTAN equivalent remaining in the animals was less than 1 percent of the administered dose.

37

Table 2. Tissue Distribution of Radioactivity in Rats 72 Hours After Oral Dosing With ^{14}C-SUTAN at 100 mg/kg

Organ/Tissue		PPM (Sutan Equivalents per gram Weight of Specimen)[a]	% of Dose
Bladder		0.498 ± 0.214	< 0.001
Muscle		0.142 ± 0.040	0.001 ± 0.0008
Stomach		0.556 ± 0.291	0.004 ± 0.0026
Spleen		0.509 ± 0.163	0.002 ± 0.0005
Heart		0.308 ± 0.082	0.001 ± 0.00
Liver		1.715 ± 0.626	0.078 ± 0.0432
Bone		0.170 ± 0.045	0.001 ± 0.0003
Lung		0.895 ± 0.255	0.006 ± 0.0016
Kidney		0.802 ± 0.149	0.007 ± 0.0022
Caecum		0.460 ± 0.259	0.004 ± 0.0026
Intestine:	Prox.	0.689 ± 0.409	0.015 ± 0.0118
	Dist.	1.482 ± 1.090	0.030 ± 0.0325
Brain		0.185 ± 0.057	0.001 ± 0.0005
Gonad		0.377 ± 0.280	0.003 ± 0.0015
Fat		0.610 ± 0.349	< 0.001
Carcass		0.392 ± 0.139	0.233 ± 0.0671
Skin		0.524 ± 0.092	0.075 ± 0.0256
Blood		1.275 ± 0.785[b]	unspecified
TOTAL			0.476 ± 0.115%

[a] Values are average of two male and two female rats. Data excerpted from Table III of the Report.

[b] Most of the radioactivity in blood was included in the carcass value.

Acc No.: 250645
MRID No.: 00129397
Tox. Chem No.: 434 A

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

005124
007778

MAY 16 1986

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

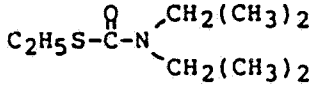
SUBJECT: Review of a Rat Metabolism Study of [1-^{14}C-isobutyl] BUTYLATE

TO: Robert Taylor
Product Manager
Registration Division(TS-767)

THRU: Jane E. Harris, Ph.D 5/15/86
Section Head, Section VI
Toxicology Branch
Hazard Evaluation Division (TS-769)

FROM: William F. Sette, Ph.D. William F. Sette 5/14/86
Environmental Protection Specialist
Toxicology Branch
Hazard Evaluation Division (TS-769)

Chemical: Butylate, Sutan, R-1910
S-ethyl-diisobutylthiocarbamate



Study: Acute oral and intraperitoneal study of urinary metabolites of [1-^{14}C-isobutyl] Butylate

Identification: Metabolism of [1-ISOBUTYL-^{14}C] SUTAN in the rat: Urinary Metabolite Identification. J.H. Ross, D.L. Bova-Thomas, J.J. Osuna, and D.J. Bowler. Stauffer Chemical Company, Mountain View, CA 94042 PMS-108, MRC 83-06, June 1983. Accession No. 250645

Registrant: Stauffer Chemical Company
Mountain View, CA 94042

34
175

Conclusions:

Following an acute oral dose of roughly 100 mg/kg, 94% of the dose was excreted within 24 hours, with 73.5% found in urine. After 48 hours, all(101.7%) of the label was recovered with 79.4% in urine, 10.5% in feces, 5.0% in cage wash, and 6.8% in volatile amines.

Eleven metabolites were identified, of which isobutyl amine (XX) and its hydroxyl derivatives (XVII,XIX) accounted for 65-75% of the urinary label.

Sulfoxidation followed by hydrolysis or glutathione conjugation was considered the major (63.5%) metabolic pathway , alpha and beta oxidation of the ethyl moiety was proposed as a second pathway, and hydroxylation of isobutyl carbons a concurrent reaction in both pathways.

This study of the excretion and metabolites of [1-^{14}C isobutyl] Butylate addresses a data gap identified in the registration standard (Attachment G 7/6/83). It complements a previous study (Thomas et al.,1979) of the distribution and carbon balance of [1^{14}C isobutyl] Butylate. This study was in progress when the other studies were submitted.

Two previous studies of the distribution, excretion, and metabolites of [1^{14}C ethyl] Butylate (Bova et al., 1978; Thomas et al.,1980) were declared invalid because the ethyl label did not follow the "core" of the molecule and the label wound up in the carbon pool of the rats.

The major deficiencies of this study of [1-^{14}C-isobutyl] Butylate were that only one dose was used and tissue distribution was not measured. However, in a previous study, tissue distribution was assayed after a 72 hour sacrifice and found to be minimal (Thomas et al.,1979). In most other respects, the study was well conducted and the data appear valid. Together with the recommended studies, these data may be reclassified.

Core Classification: Supplementary.

Recommendation: The registration standard (7/6/83) identifies the lowest effect level (LEL) for Butylate as 80 mg/kg/day and the no-effect level (NOEL) as 20 mg/kg/day based on the chronic mouse study. The doses used in the present studies, roughly 100 mg/kg, represent a high dose by this criterion. What is needed are metabolism studies of [1-^{14}C-isobutyl] Butylate at a low dose, and repeated low doses. Taken together with the present data, these studies should satisfy the metabolism requirement.

35

Butylate toxicology review

Page _____ is not included in this copy.

Pages 36 through 38 are not included in this copy.

The material not included contains the following type of information:

___ Identity of product inert ingredients

___ Identity of product 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.