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39003

CASWELL FILE

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

010977

SEP 30 1988

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Metam sodium. The biokinetics and metabolism of ^{14}C-metam sodium in the rat. Possible use of studies with ^{14}C-dazomet and ^{14}C-methyl-isothiocyanate to support the metam sodium application.

EPA ID No. 039003 Project No. 8-0962
Caswell No. 780 Accession No. 406410-00

FROM: Sidney Stolzenberg, Ph.D.
Review Section I
Tox Branch-HFAS/HED (TS-769 C)
Sidney Stolzenberg 9/28/88

THRU: Quang Q. Bui, Ph.D., D.A.B.T.
Head, Review Section I
Tox Branch-HFAS/HED (TS-769 C)
Quang Bui 9/28/88

and

William L. Burnam
Acting Deputy Division Director
Health Effects Division
W L Burnam 9/30/88

TO: Geraldine Werdig, Chief
Data Call In Staff
Registration Division (TS-767 C)

Registrant:

ICI Americas
Wilmington, DE 19817

on behalf of the Metam Sodium Task Force

Action Requested:

Review animal metabolism studies in support of Data Call-In-Notice of 9/28/84 for metam sodium.

Recommendation:

We agree with the applicant that the studies with dazomet and methyl-isothiocyanate (MITC) support the pharmacokinetic and

metabolism data for metam sodium. It should not be necessary, for example, to repeat pharmacokinetic and metabolism studies done for dazomet that were not done for metam sodium. These would include biliary excretion studies and multiple 7 or 15 consecutive day oral dose studies. Although the metabolic profile of components excreted in urine and air, tissue distribution as well as metabolic profiles observed in liver and kidneys were similar after administration of single oral doses of all 3 compounds, there were some important differences, mainly quantitative in nature.

Toxicology defers to RCB for analyses of the studies on the conversions of metam sodium and dazomet to MITC when applied to crops in the field.

Group A studies, which involves intravenous administration of test compound, have not been performed with metam sodium, dazomet or MITC. This requirement for may be waived because exposure to metam sodium would be expected to be mainly oral, in food.

Classifications:

Metam sodium

Group A. Single i.v. labelled dose. Not performed
Group B. Single oral low dose with labelled compound. Acceptable.
Group C. Single daily oral doses of non-labelled compound for 14 days followed at 24 hours after the last dose with a single oral labelled dose. Not performed.
Group D. Single oral high dose with labelled compound. Acceptable.

Dazomet

Group A. Single i.v. dose with labelled compound. Not performed.
Group B. Single oral low dose with labelled compound. Acceptable
Group C. Single daily oral doses of non-labelled compound for 14 days followed at 24 hours after the last dose with a single oral labelled dose. Acceptable
Group D. Single oral dose of labelled compound at high dose. Acceptable

Methyl isothiocyanate.

Group A. Single i.v. labelled dose. Not performed.
Group B. Single oral labelled dose. Acceptable.
Group C. Single daily oral doses of non-labelled compound for 14 days followed at 24 hours after the last

dose with a single oral labelled dose. Not performed.

Group D. Single oral high dose with labelled compound. Acceptable.

Comment: Based on our suggestion that the studies with dazomet and MITC support the pharmacokinetic and metabolism studies with metam sodium, we consider that the Group C studies with metam sodium are satisfied.

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Primary Reviewer: Sidney Stolzenberg, Ph.D.
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Secondary Reviewer: Quang Q. Bui, Ph.D., D.A.B.T.
Head, Review Section I, Toxicology Branch - Herbicide, Fungicide, and Antimicrobial Support
Health Effects Division (TS-769C)

DATA EVALUATION REPORT

Study Type: Metabolism
Guideline No.: 85-1

Study Title: The Biokinetics and Metabolism of ^{14}C-Metam Sodium in the Rat

EPA Identification Numbers: EPA ID No. 039003
Caswell No.: 780
Project No.: 8-0962
Accession No.: 406410-00

Submitted by: ICI Americas, Inc.
Wilmington, DE 19897
for the Metam Sodium Task Force Consortium

Testing Laboratory: Huntingdon Research Centre
Huntingdon, Cambridgeshire, England

Study Authors: D.R. Hawkins, L.F. Elsom, and G. Girkin

Study ID No.: HRC/BSF 455/6/7/8875

Completion Date: November 12, 1987

Conclusions: Summary

Pharmacokinetic and metabolism studies in rats for dazomet, metam sodium and methyl-isothiocyanate (MITC) were submitted to support a metabolism study (85-1) for metam sodium. Although there are substantial differences in chemical structure between the three compound, it is claimed that both metam sodium and dazomet produce high levels of MITC in the soil. Futhermore, MITC is considered to be a key intermediary in the metabolism of both metam sodium and dazomet in the rat (see proposed schematic on page 3 of this review).

The data from tests with all 3 compounds were submitted to support the application for metam sodium. Each compound was tested at two dose levels in rats. It was shown that all 3 compounds were excreted mainly in urine with urinary recoveries over 168 hours of 63 to 65% for dazomet 37 to 58% for metam sodium and 84 to 87% for MITC at both dose levels. Excretion via the feces was low, usually ranging between 1.5 to 3.3% at both doses for all 3

compounds. Three different compounds were found to be excreted via the lungs as metabolic products which included MITC, CO_2 and COS/CS_2. Total excretion of the 3 products via the lungs over a 72 hour collection period were about 35 and 50% for low and high dose metam sodium, 22 and 28% for low and high dose dazomet, 22 and 9% for low and high dose MITC, respectively. There were no differences between males and females in amounts excreted via the three routes. Tissue retention at 168 hours was about 2% for all 3 compounds at both dose levels. Total recoveries, including the percentage of the doses excreted and that remaining in the tissues combined after 168 hours, ranged from 92.6 to 106%, indicating virtually complete absorption from the G.I. tract. By the first 24 hours, 85% or more of each of the 3 compounds at both dose levels had been excreted. All 3 compounds were also rapidly absorbed from the G.I. tract with plasma t_{max} between 0.25 to 1.0 hours. However, plasma half-lives after 24 hours were long, ranging from around 60 to 74 hours for all 3 compounds. Tissue and plasma levels at all time periods, and plasma AUC's, were consistently higher in females than in males by a substantial amount, suggesting that this compound may be more toxic to female rats. The tissue with the highest uptake for all 3 compounds was the thyroid gland. High uptake were also seen by the liver, kidneys and lung, with lowest levels in testes, brain and eyes. Metabolic profiles detected in urine, liver and kidneys were basically similar for the three compounds but there were some differences, mainly quantitative in nature.

The data appear convincing that both dazomet and metam sodium form MITC during the early stages of metabolism in rats. The proposed metabolic pathway involving these three compounds is shown on page 3 of this review. Only 2 metabolites, M2 and M5 are considered to be unequivocally identified. A suggested structure based on limited data is proposed for a third metabolite, M4. On the basis of these data, the applicant has concluded that metam sodium and dazomet "exhibit an extremely similar kinetic profole in the rat" and MITC is produced in the metabolism of both compounds. Therefore, the applicant feels justified in their decision to forgo additional metabolism studies with metam sodium.

Although the metabolic profiles detected in urine, liver and kidneys were similar and tissue distribution were similar for the three compounds, there were some differences, mainly quantitative in nature. Substantial quantitative differences were seen in products of respiration, tissue distribution of radioactivity, components found in urine, liver and kidneys.

Classification:

Dazomet.

Group A. Single i.v. dose with labelled compound. Not performed.

Group B. Single oral low dose with labelled compound. Acceptable

Group C. Single daily oral doses of non-labelled compound

for 14 days followed at 24 hours after the last dose with a single oral labelled dose. Acceptable

Group D. Single oral dose of labelled compound at high dose. Acceptable

Metam Sodium.

Group A. Single i.v. labelled dose. Not performed
Group B. Single oral low dose with labelled compound. Acceptable.
Group C. Single daily oral doses of non-labelled compound for 14 days followed at 24 hours after the last dose with a single oral labelelled dose. Not performed.
Group D. Single oral high dose with labelled compound. Acceptable.

Methyl isothiocyanate.

Group A. Single i.v. labelled dose. Not performed.
Group B. Single oral labelled dose. Acceptable.
Group C. Single daily oral doses of non-labelled compound for 14 days followed at 24 hours after the last dose with a single oral labelled dose. Not performed.
Group D. Single oral high dose with labelled compound. Acceptable.

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Introduction:

The report was originally written by BASF Antiengesellschaft, West Germany, and is presently being submitted on behalf of BASF Corporation, Buckman Laboratories, Stauffer Chemical Company, Transbas, Inc.,.and UCB Chemicals Corporation.

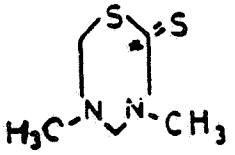
The package was submitted in response to the Data Call-In Notice of May 19, 1986 for metam sodium. Even though the title suggests that the report pertains only to metam sodium, it contains biokinetics and metabolism studies for three separate compounds in three separate sections of the report. The three compounds studied and the two doses at which each was studied in rats by oral intubation were as follows:

	Dose 1		Dose 2	
Substance	mg/kg	Mol/kg	mg/kg	Mol/kg
Metam sodium	10	7.7×10^{-5}	100	7.7×10^{-4}
Dazomet	10	6.2×10^{-5}	100	6.2×10^{-4}
MITC	4.4	6.0×10^{-5}	33	4.5×10^{-4}

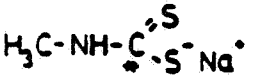
The high dose for each compound was considered a "toxic effect level."

All three studies were performed by Huntingdon Research Centre in England.

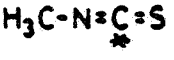
The structure of these compounds are as follows:



Dazomet



Metam sodium



MITC

It is claimed that metam sodium and dazomet produce a high amount of methyl-isothiocyanate (MITC) in the soil. Also, both dazomet and metam sodium are converted to MITC in the metabolic pathways of rats.

The following is the suggested pathway of metabolism in rats with all three of these compounds shown fitting into the scheme.

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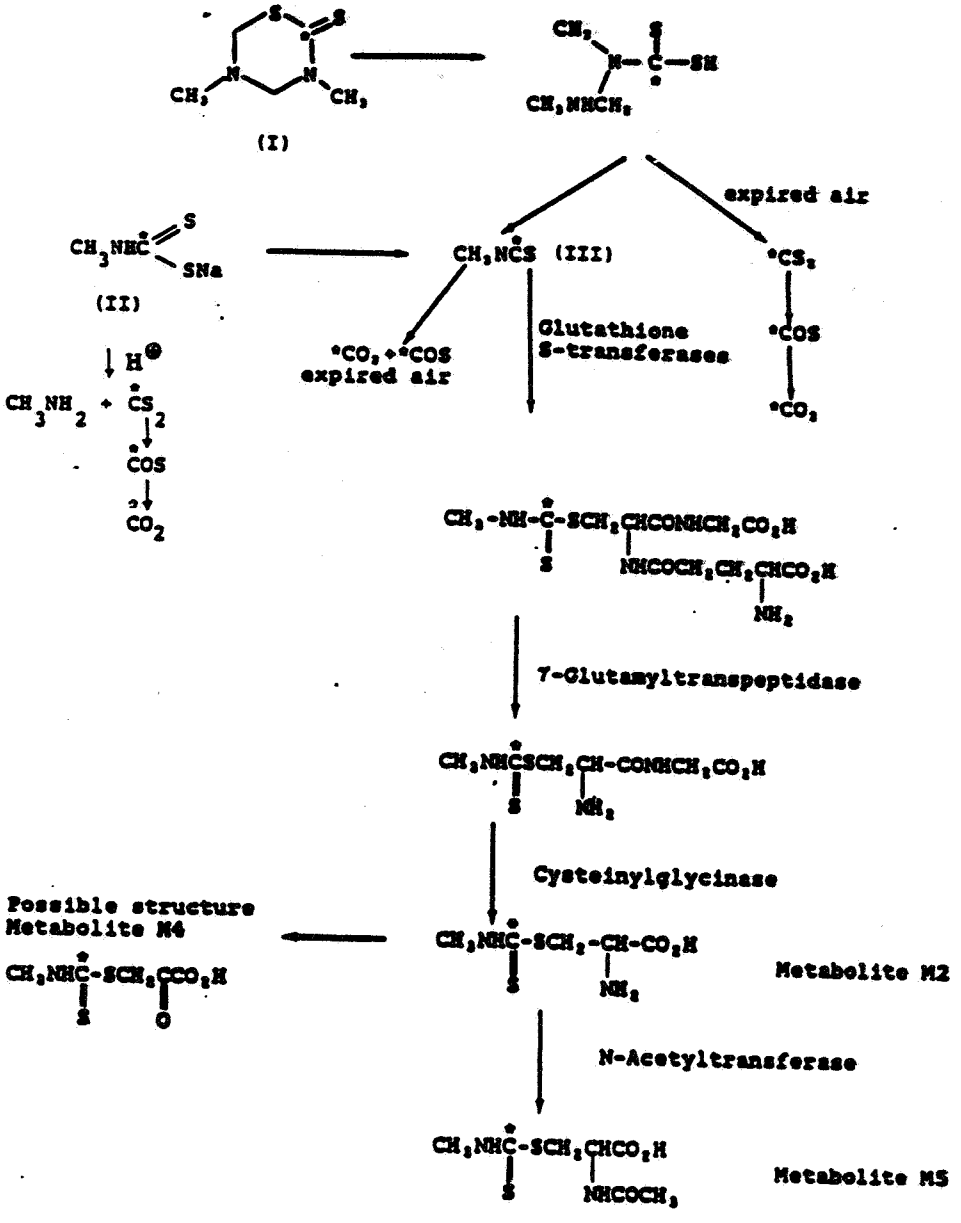
SCHEME I

Postulated metabolic pathway for ^{14}C-dazomet (I), ^{14}C-metam sodium (II) and methyl isothiocyanate-^{14}C (III) in the rat



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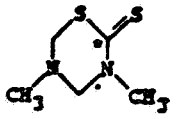
This report is divided into three parts. Each part consists of a set of pharmokinetic and metabolism studies for each of the three compounds.

Part I. The Biokinetics and Metabolism of ^{14}C-Dazomet in the Rat

A. Materials

1. Radioactive dazomet

The structure of dazomet and position of ^{14}C in the compound used in the studies is as follows:



Dazomet

Chemical Name: Tetrahydro-3,5-dimethyl-2H-1,3,5-thiadiazin-2-thion

Molecular Weight: 162.3

The nonradioactive material used was claimed to have a purity of 99.3 percent, determined by HPLC. The compound is claimed to be stable with no decomposition products detected after 2 years of storage in the dark at 25 °C in a dessicator. Radiochemical purity of the ^{14}C-dazomet was 97 percent, determined by TLC with three solvent systems.

Specific activities were as follows:

Substance	Radioactivity (uCi/mg)
Pure compound	79.5
Low dose	3.78
High dose	0.419
Tissue Metabolite study	1.52

2. Vehicle Used for Dosing

Carboxymethylcellulose, 1% aqueous suspension.

3. Doses

10 and 100 mg/kg for single-dose studies, 10 mg/kg/day for 14-day dosing study.

4. Stability of Dosage Forms

No experiments appeared in this report on stability or homogeneity of the carboxymethylcellulose suspensions. There was no statement on how long the dosage forms were stored prior to administration.

5. Route of Administration

By oral intubation.

6. Animals Used

Sprague-Dawley rats, Crl:COBS(SD)CD strain of Charles River, UK. Males were 7 weeks old, females were 9 weeks old, body weight for both sexes was about 200 g.

B. Procedures

1. Collection of Expired Air in Excretion-Metabolism Studies.

Expired air was passed through a series of three traps; 2-ethoxyethanol for collection of methyl isothiocyanate, NaOH for trapping CO_2, and Viles reagent (ethanol-diethylamine-triethanolamine) for collection of COS and/or CS_2.

2. Preparation of Materials for Measurements of Radioactivity by Combustion Analysis.

Carcasses were digested in methanol-triton-405 and NaOH. Tissues were minced and homogenized. Feces were homogenized in distilled water.

3. Preparation of Materials for TLC or HPLC Analyses of Components

a. Urine and Bile

Urine from intact rats given the 100 mg/kg dose and bile samples collected from cannulated bile ducts were subjected to hydrolysis with B-glucuronidase containing aryl sulphatase (from Helix pomatia). Both enzyme hydrolyzed and nonhydrolized vacuum concentrated urine and bile preparations were subjected to a sequence of solvent extractions, evaporation of solvents and subjected to HPLC and/or TLC.

b. Liver and Kidney Homogenates

These were extracted three times with methanol and the combined extracts were concentrated under an N_2 stream at 37 °C. Radioactivity recoveries ranged from 67 to 84 percent in the extracts. Aliquots of the concentrates were subjected to TLC for metabolite analysis.

4. Analysis of Radioactivity

Radioactivity was measured in a liquid scintillation counter using counts at least twice background. TLC plates were subjected to an automatic TLC-linear analyzer.

5. Identification of Metabolic Components

Radioactive areas on TLC developed plates were removed, eluted with solvents, concentrated, and subjected to further purification with HPLC. These were subjected to mass spectra analysis.

The mass spectra of three chemically synthesized components were compared to three isolated and purified TLC components in urine for final identification of the metabolites.

Compliance

- A signed statement of Confidentiality Claim was included.
- A signed statement of compliance with EPA's GLP was provided.
- A signed Quality Assurance Statement was provided.

Preliminary Excretion-Retention Study

Two of each sex received 10 mg/kg, single dose by intubation. Urine and feces were collected over a 120-hour period, trapped air contents were collected for a period of 72 hours. A summary of all the results, photocopied from Appendix 7, is shown on the page which follows.

Total urinary excretion was about 67 to 70 percent, total fecal excretion was around 3 percent for both sexes. Most of the excreted radioactivity in urine, air, and feces was found within the first 24 hours. Trap 1 for methyl isothiocyanate contained 1 to 2 percent of the radioactivity, trap 2 for CO_2 had 15 to 19 percent, whereas trap 3 for COS and CS_2 had 2 to 4 percent over the 72-hour collection period. Total recoveries in feces, urine, and expired air combined was about 92 to 96 percent.

APPENDIX 7

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Preliminary excretion study

TABLE 1

Excretion of radioactivity by rats after single oral doses of ^{14}C-dasomet at a dose level of 10 mg/kg

Results are expressed as % dose

Animal no.	AM	BM	Mean males	CF	DF	Mean females
Urine						
0 - 24	61.72	62.06	61.89	65.48	64.25	64.87
24 - 48	3.22	3.42	3.32	2.89	3.90	3.40
48 - 72	1.07	1.11	1.09	0.95	1.08	1.02
72 - 96	0.67	0.61	0.64	0.52	0.55	0.54
96 - 120	0.36	0.46	0.41	0.35	0.37	0.36
Total urine	67.04	67.66	67.35	70.19	70.15	70.17
Cage washings	0.15	0.15	0.15	0.10	0.12	0.11
Faeces						
0 - 24	1.05	2.94	2.00	2.32	2.52	2.42
24 - 48	0.48	0.52	0.50	0.38	1.00	0.69
48 - 72	0.43	0.18	0.31	0.17	0.08	0.13
72 - 96	0.17	0.10	0.14	0.09	0.15	0.12
96 - 120	0.05	0.09	0.07	0.05	0.07	0.06
Total faeces	2.18	3.83	3.01	3.01	3.82	3.42
Expired air trap 1						
0 - 6	0.98	0.03	0.51	1.70	1.35	1.53
6 - 24	0.23	0.22	0.28	0.46	0.47	0.47
24 - 48	0.09	0.15	0.12	0.10	0.28	0.19
48 - 72	0.04	0.06	0.05	0.03	0.07	0.05
Total trap 1	1.34	0.56	0.93	2.29	2.17	2.23
Expired air trap 2						
0 - 6	14.72	11.64	13.18	9.24	6.79	8.02
6 - 24	4.19	5.17	4.68	5.55	7.65	6.60
24 - 48	0.81	0.66	0.74	0.70	0.93	0.82
48 - 72	0.26	0.29	0.28	0.24	0.31	0.28
Total trap 2	19.98	17.76	18.87	15.73	15.68	15.71
Expired air trap 3						
0 - 6	2.19	1.52	1.86	2.58	1.05	1.82
6 - 24	0.15	0.29	0.22	1.39	2.88	2.14
24 - 48	<0.02	<0.02	-	0.03	0.07	0.05
48 - 72	<0.02	<0.02	-	<0.02	<0.02	-
Total trap 3	2.34	1.81	2.08	4.00	4.00	4.00
Total traps 1 - 3	23.66	20.13	21.90	22.02	21.85	21.94
Total recovery	93.03	91.77	92.40	95.32	95.94	95.63

The data in this table have been checked for accuracy by [illegible]

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Main Excretion-Retention Study

For the single-dose studies, five of each sex received 10 or 100 mg/kg. For the multiple dose test, five male and five female rats first received 14 daily doses of nonlabeled dazomet at 10 mg/kg/day and on day 15 received 10 mg/kg of ^{14}C-labeled dazomet. In both the single and multiple dose studies, urine and fecal samples were obtained each day up to 7 days (168 hours) following the radioactive dose. Expired air samples were obtained at 24-hour intervals up to 72 hours. Samples of blood were obtained just before killing at 168 hours and organs listed below in Table 3 after killing.

TABLE 1

Mean excretion and retention of radioactivity by male and female rats after single oral doses of ^{14}C-dazomet at dose levels of 10 and 100 mg/kg and after 14 daily doses of dazomet followed by a single dose of ^{14}C-dazomet at a dose level of 10 mg/kg/day

Results are expressed as % dose

Dose regime	Single 10 mg/kg		Single 100 mg/kg		Repeated 10 mg/kg	
	Male	Female	Male	Female	Male	Female
Tissues	2.72	2.31	2.23	2.40	2.42	2.19
Urine (0 - 168 hours)	68.18	68.79	66.53	62.54	62.67	65.43
Cage washings	0.19	0.12	0.09	0.11	0.07	0.07
Feeces (0 - 168 hours)	3.28	3.08	2.48	2.28	3.50	2.81
Expired trap 1 (0 - 72 hours)	1.06	1.55	1.29	2.08	0.56	1.10
Expired trap 2 (0 - 72 hours)	17.76	15.99	11.50	11.15	18.52	17.51
Expired trap 3 (0 - 72 hours)	2.87	5.58	14.81	19.47	2.77	3.72
Total recovery	96.85	97.34	98.94	100.00	90.59	92.83

The data in this table has been checked for accuracy by the reviewer.

In Table 1, taken from the report, tissue retention (carcass plus all organs combined) came to 2.2 to 2.7 percent of the radioactive dose for both sexes with both the low or high dose as well as with the 15 daily doses. Urinary excretion over the 168-hour period, including the cage washings, amounted to 62.3 to 68.9 percent of dose for males or females for all three treatment regimens with no differences between sex, dose, or single vs. continuous daily dosing. Fecal excretion amounted to approximately 3 percent of the dose in males and females for all three regimens. The slightly lower excretion rate in the 100 mg/kg treated groups was evidently not considered to be different. The radioactivity found in air trap 1 (methyl isothiocyanate) was about 1 to 2 percent with no differences between the 3 regimens seen. However, for the 100 mg/kg treated group, the amount of radioactivity in air trap 2 (CO_2) was lower but for trap 3 (COS/CS_2) it was higher than for the 10 mg/kg group. Recoveries in the three air traps for the multiple day treated animals were about the same as for the single dose 10 mg/kg group. Total excretion in 7 days (total recovery minus amount in the tissues as seen in Table 1) amounted to 88.2 to 97.6 percent with no difference between the high and low doses.

Table 2 which follows, taken from the submitted report, shows the excretion pattern by the time collection periods. The total amount recovered within the first 24 hours of dosage in urine, feces, and in the three air traps combined was about 79.3 to 85.6 percent of the dose with no apparent difference between the two dose levels or the 15-day treatment regimen. However, more CO_2 but less COS and/or CS_2 was recovered in the 100 mg/kg treated rats.

Mean concentration of radioactivity found in the organs of the rats killed at 168 hours after the single doses or after the last of 15 doses is shown in Table 3, taken from the report (See page 11). The organ of highest uptake was the thyroids. High levels were also found in liver and kidneys. Lungs had a high level which was about 1/2 that foundin liver or kidneys. The latter three organs are considered to be the organs of excretion or biotransformation. Organ concentrations were also relatively high in ovaries, adrenals, and whole blood. There appeared to be no increased amount of radioactive compound in organs of the multiple dose treated rats compared to the single dose 10 mg/kg group. With the exception of liver, concentrations in all organs were higher in females than in males.

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TABLE 2

Mean excretion of radioactivity in the urine, faeces and expired air of male and female rats after single oral doses of ^{14}C-dazomet at dose levels of 10 and 100 mg/kg and after 14 daily oral doses of dazomet followed by a single dose of ^{14}C-dazomet at a dose level of 10 mg/kg/day

Results are expressed as % dose

Dose regime	Single 10 mg/kg		Single 100 mg/kg		Repeated 10 mg/kg	
	Male	Female	Male	Female	Male	Female
Urine						
0 - 8	39.59	33.50	16.73	14.53	40.64	32.36
8 - 24	23.22	29.32	42.70	35.05	16.83	27.75
24 - 48	2.53	3.33	4.98	10.20	2.69	2.92
48 - 72	1.10	1.07	0.89	1.54	1.02	1.01
72 - 96	0.61	0.59	0.47	0.52	0.55	0.57
96 - 120	0.50	0.42	0.33	0.28	0.37	0.34
120 - 144	0.33	0.28	0.24	0.23	0.29	0.26
144 - 168	0.30	0.27	0.19	0.19	0.27	0.22
Faeces						
0 - 24	2.37	1.74	0.67	0.67	2.39	1.42
24 - 48	0.54	0.80	1.49	1.26	0.78	0.87
48 - 72	0.14	0.32	0.17	0.16	0.21	0.31
72 - 96	0.07	0.09	0.06	0.07	0.09	0.06
96 - 120	0.06	0.05	0.04	0.04	0.05	0.06
120 - 144	0.04	0.04	0.03	0.03	0.04	0.05
144 - 168	0.04	0.04	0.02	0.02	0.04	0.03
Expired air trap 1						
0 - 24	0.96	1.35	1.03	1.56	0.49	0.99
24 - 48	0.07	0.16	0.19	0.39	0.06	0.08
48 - 72	0.03	0.04	0.06	0.13	0.01	0.03
Expired air trap 2						
0 - 24	16.60	14.61	10.10	8.72	17.41	16.31
24 - 48	0.92	1.14	1.17	2.04	0.86	0.92
48 - 72	0.25	0.25	0.23	0.39	0.25	0.28
Expired air trap 3						
0 - 24	2.78	5.38	14.33	18.78	2.72	3.65
24 - 48	0.06	0.12	0.46	0.65	0.05	0.07
48 - 72	<0.02	<0.02	0.02	0.04	<0.03	<0.03
Total excreted during the first 72 hours in urine, faeces and air traps combined.	85.5	80.5	85.6	79.3	80.5	82.5

The data in this table has been checked for accuracy by the reviewer.

TABLE 3

Mean concentrations of radioactivity in the tissues of male and female rats sacrificed at 168 hours after single oral doses of ^{14}C-dazomet at dose levels of 10 and 100 mg/kg and after 14 daily doses of dazomet followed by a single dose of ^{14}C-dazomet at a dose level of 10 mg/kg/day

Results are expressed as µg equivalents ^{14}C-dazomet/g

Dose regime	Single 10 mg/kg		Single 100 mg/kg		Repeated 10 mg/kg	
	Male	Female	Male	Female	Male	Female
Tissues						
Eyes	0.092	0.107	0.75	1.13	0.110	0.125
Brain	0.088	0.107	0.68	0.93	0.083	0.093
Adrenal glands	0.295	0.292	3.03	3.25	0.548	0.419
Bone marrow	0.088	<0.201	<0.80	<1.60	<0.114	<0.236
Thyroid gland	2.29	5.03	14.0	18.9	2.62	5.97
Muscle	0.094	0.117	0.60	0.86	0.096	0.108
Fat	0.080	0.057	0.54	0.50	0.098	0.066
Pancreas	0.109	0.131	0.79	1.16	0.121	0.143
Lungs	0.444	1.06	3.18	7.05	0.411	0.813
Ovaries	-	0.456	-	3.93	-	0.408
Testes	0.042	-	0.31	-	0.047	-
Uterus	-	0.113	-	1.03	-	0.104
Spleen	0.092	0.128	0.86	1.67	0.107	0.137
Kidneys	0.901	1.57	6.92	13.4	0.874	1.53
G.I. tract	0.094	0.111	0.44	0.85	0.098	0.134
Liver	1.02	0.311	6.21	2.14	1.17	0.378
Whole-blood	0.205	0.299	2.37	3.70	0.242	0.295
Plasma	0.045	0.075	0.25	0.43	0.054	0.072
Heart	0.194	0.292	1.28	2.14	0.185	0.256
Carcass	0.197	0.249	1.86	2.70	0.208	0.234

G.I. tract Gastro-intestinal tract

The data in this table has been checked for accuracy by the reviewer.

Biliary Excretion

Bile duct cannulated rats, three of each sex per dose level, received 10 or 100 mg/kg, single oral doses. Bile samples were collected at 3-hour intervals, urine and feces at 24-hour intervals, over a 48 hour period. Biliary excretion rates, expressed as percent of dose and cumulative percent of dose, are shown in Table 23, copied from the applicant's report. The highest rates of excretion into bile were generally observed within the first 6 to 9 hours after dosing. The investigators concluded that biliary excretion played a minor role in elimination of the compound.

Comment: When compared to the total excreted in the feces, which was substantially higher even after only 24 hours in bile than in the entire 168 hour fecal collection of intact rats at both dose levels, it suggests that there was enterohepatic recirculation of radioactive compounds. However, this may be an artifact due to bile duct cannulation.

TABLE 23

Mean excretion of radioactivity in bile by rats with cannulated bile ducts after single oral doses of ^{14}C-daxonet at dose levels of 10 and 100 mg/kg

Results are expressed as % dose and cumulative % dose

Time (hours)	Single 10 mg/kg				Single 100 mg/kg			
	Male		Female		Male		Female	
	% dose	Cumulative % dose	% dose	Cumulative % dose	% dose	Cumulative % dose	% dose	Cumulative % dose
0 - 3	1.36	1.36	1.62	1.62	1.09	1.09	0.86	0.86
3 - 6	2.03	3.39	0.93	2.55	0.63	1.72	0.61	1.47
6 - 9	1.98	5.37	1.07	3.62	0.43	2.15	0.39	1.86
9 - 12	1.43	6.80	0.94	4.55	0.41	2.56	0.39	2.25
12 - 15	0.60	7.40	0.79	5.34	0.62	3.18	0.44	2.68
15 - 18	0.30	7.70	0.43	5.77	0.65	3.83	0.59	3.27
18 - 21	0.16	7.86	0.19	5.96	0.74	4.57	0.65	3.92
21 - 24	0.09	7.95	0.15	6.11	0.75	5.32	0.64	4.56
24 - 27	0.07	8.02	0.10	6.22	0.62	5.94	0.54	5.10
27 - 30	0.05	8.07	0.07	6.29	0.51	6.45	0.52	5.62
30 - 33	0.04	8.12	0.05	6.34	0.24	6.68	0.32	5.94
33 - 36	0.03	8.15	0.04	6.38	0.13	6.81	0.17	6.11
36 - 39	0.03	8.18	0.03	6.41	0.09	6.90	0.13	6.24
39 - 42	0.03	8.21	0.03	6.44	0.06	6.95	0.08	6.32
42 - 45	0.02	8.23	0.02	6.46	0.04	6.99	0.07	6.39
45 - 48	0.02	8.24	0.01	6.47	0.04	7.03	0.06	6.45

The data in this table has been checked for accuracy by the reviewer.

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The data in Table 22, taken from the report, confirm that the primary route of excretion was via the urine, even in the bile duct cannulated rat.. It also shows the retention in liver, G.I. tract and carcass in the bile duct cannulated rats killed at 48 hours after dosing.

TABLE 22

Mean excretion and retention of radioactivity by rats with cannulated bile ducts after single oral doses of ^{14}C-dazomet at dose levels of 10 and 100 mg/kg

Results are expressed as % dose

Dose regime	Single 10 mg/kg		Single 100 mg/kg	
	Male	Female	Male	Female
Tissues				
Liver	1.57	0.39	1.13	0.47
G.I. Tract	0.34	0.30	0.36	2.16
Carcass	3.53	3.99	3.00	5.65
Bile				
0 - 24 hour	7.95	6.11	5.32	4.56
24 - 48 hour	0.29	0.36	1.71	1.89
Urine				
0 - 24 hour	49.35	50.02	27.43	34.93
24 - 48 hour	2.75	3.18	13.04	13.19
Cage washings	0.32	0.34	1.61	1.32
Faeces				
0 - 24 hour	2.50	1.35	0.97	0.14
24 - 48 hour	0.76	1.60	1.86	0.45
Total recovery	69.38	67.65	56.43	64.77

The data in this table has been checked for accuracy by the reviewer.

Plasma Concentrations

Five rats of each sex received 10 or 100 mg/kg, single oral dose and blood samples were taken from the tail at the time intervals listed in Table 41, taken from the applicant's report.

TABLE 41

Mean concentrations of radioactivity in the plasma of rats after single oral doses of ^{14}C-dazomet at dose levels of 10 and 100 mg/kg

Results are expressed as µg equivalents ^{14}C-dazomet/ml

Dose regime	Single 10 mg/kg		Single 100 mg/kg	
	Male	Female	Male	Female
Plasma				
Pre-dose	<0.032	<0.032	<0.30	<0.30
0.25	0.918	1.46	11.6	16.7
0.5	1.36	1.76	9.40	16.9
1	1.60	2.07	10.3	13.1
2	1.42	1.55	8.74	10.6
4	1.15	1.14	5.98	10.6
6	1.01	1.15	5.59	10.9
24	0.417	0.469	3.64	6.31
48	0.241	0.304	1.57	2.76
72	0.201	0.262	1.08	1.80
96	0.128	0.221	0.78	1.31
120	0.103	0.203	0.61	1.07
168	0.064	0.139	0.39	0.75
240	<0.032	0.048	<0.30	<0.30

The data in this table has been checked for accuracy by the reviewer.

At low dose, t_{max} occurred at 1 hour for both males and females, whereas at high dose t_{max} was 0.25 and 0.5 hour for males and females, respectively. Terminal $t_{1/2}$ after 24 hours was reported to be 61 and 69 hours for males and females at low dose, 61 and 71 hours for males and females at high dose.

It is important to note that at both dose levels, mean plasma levels were higher in females than in males at virtually every time period. Plasma levels became about twice as high in males than in females at 96 hours or later with low dose, and was generally at least 50 percent higher in females than in males at high dose at most time periods after dosing.

The following is a summary of pharmokinetic data derived from the rat plasma levels, which were extracted from Tables 42 to 45 of the applicant's report.

Dose	10 mg/kg				100 mg/kg			
Sex	Males		Females		Males		Females	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
T1	48.00	00.00	76.80	10.73	48.00	00.00	57.60	13.15
T1	168.00	0.00	240.00	0.00	168.00	0.00	168.00	0.00
T0.5	60.9	0.9	68.7	10.7	60.8	3.9	71.1	10.4
reg	0.986	0.009	0.972	0.030	0.984	0.011	0.976	0.022
AUCO	44.0	3.4	64.7	8.2	283.8	16.4	494.1	51.0

T1 is the entered terminal slope start time (hours).
T2 is the entered terminal slope end time (hours).
T0.5 is the terminal half-life (hours).
reg is the regression coefficient (r) of the fitted line.
AUCO is the area under the normal curve without extrapolation (ug/mL.hours).
SD is standard deviation.

The increase in dose level had no apparent effects on terminal elimination slopes or half-lives. In females, AUC was 47 percent higher at low dose and 74 percent higher at high dose than in males.

Tissue Distribution Studies

A. Quantitative Studies

Five of each sex received 10 or 100 mg/kg of radio-labelled substance each day for 7 consecutive days and one of each sex was killed between 1 to 240 hours postdosing, at the time intervals shown in Table 46, taken from the applicant's report.

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TABLE 46

Concentrations of radioactivity in the tissues of rat, sacrificed at various times after the last of 7 daily oral doses of ^{14}C-dazomet at a dose level of 10 mg/kg/day

Results are expressed as µg equivalents ^{14}C-dazomet/g

Animal number	53♂	54♀	55♂	56♀	57♂	58♀	59♂	60♀	61♂	62♀
Sacrifice (hours)	1	1	6	6	24	24	72	72	240	240
Tissues										
Eyes	1.77	2.28	2.11	1.85	1.09	1.41	0.566	1.17	0.467	0.634
Brain	1.98	2.82	2.57	3.07	1.14	1.48	0.605	0.850	0.269	0.355
Adrenal glands	9.74	8.31	10.9	9.63	7.02	5.95	2.23	3.90	0.525	0.866
Bone marrow	3.00	4.27	3.61	4.77	1.60	2.24	0.610	1.19	0.192	0.415
Thyroid gland	97.9	85.3	108	153	91.1	52.8	11.9	69.9	7.14	33.0
Muscle	1.84	2.66	2.39	2.37	1.08	1.40	0.705	0.999	0.307	0.401
Fat	2.31	2.82	2.30	2.76	1.76	0.977	0.674	0.620	0.323	0.267
Pancreas	4.43	5.36	4.42	4.65	1.73	2.01	0.945	1.46	0.370	0.436
Lungs	7.27	13.7	8.30	13.9	4.77	10.3	2.89	6.68	1.07	3.28
Ovaries	NS	7.79	NS	12.1	NS	6.36	NS	3.65	NS	1.17
Testes	1.30	NS	1.69	NS	0.683	NS	0.339	NS	0.151	NS
Uterus	NS	3.91	NS	3.37	NS	1.96	NS	0.915	NS	0.390
Spleen	3.82	4.65	3.88	5.27	1.78	2.11	0.868	1.30	0.350	0.484
Kidneys	19.4	29.2	23.1	31.6	11.7	10.8	6.63	12.5	2.04	3.90
G.I. tract	57.0	76.1	19.9	27.0	2.22	3.19	2.97	1.15	0.424	0.407
Liver	30.9	15.0	27.9	9.23	14.3	4.82	7.26	3.58	1.91	0.674
Whole-blood	7.28	9.49	6.79	8.60	2.59	3.67	1.54	2.34	0.865	1.27
Plasma	2.19	2.94	2.08	2.35	0.922	1.28	0.462	0.721	0.117	0.172
Heart	4.42	6.34	4.50	5.23	2.36	3.16	1.27	2.33	0.445	0.861
Carcass	3.97	4.35	4.95	4.61	2.82	2.89	1.84	2.15	1.08	1.10

G.I. tract Gastro-intestinal tract
NS No sample

The data in this table has been checked for accuracy by the reviewer.

Highest concentrations in most tissues occurred at 6 hours, with the exception of G.I. tract, liver, possibly also heart and whole blood, where highest levels occurred the first hour. In all organs, except liver, higher levels occurred in females than in males at almost every time period. Highest uptake and retention was by the thyroid. The next highest levels were found in the G.I. tract, liver, kidneys, and lungs. The latter three organs are considered the organs of excretion or biotransformation. Concentrations were also relatively high in whole blood, adrenals, and ovaries. Even at 240 hours, tissue levels in all organs were higher than in plasma.

B. Autoradiography - Qualitative Distribution Study

Six males received 10 mg/kg/day for 7 days. One male was killed at 24 hours after the first dose, then at 1, 6, 24, 72, and 240 hours after the last of 7 doses and each was prepared for autoradiography.

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Photocopies of autoradiographs were submitted in Appendix I of the applicant's report. They generally confirm the quantitative studies. Table 48 which follows, taken from the applicant's report, is a summary of radioactivity distribution as graded by the investigators after visual inspection of autoradiographs.

TABLE 48

Distribution of radioactivity after oral doses to male rats and assessments made after visual inspection of whole-body autoradiographs

Tissue type	Tissue	Time of sacrifice (after last dose)					
		1 hr	6 hr	24 hr	72 hr	240 hr	24 hr single dose
Central nervous system	brain	1	1	1	1	-	1
	spinal cord	1	1	1	1	-	1
Endocrine glands	adrenal	1	1	1	1	-	1
	pituitary	1	1	1	-	-	1
	thymus	2	2	2	½	1	1
	thyroid	3	3	3	3	2	2
Exocrine glands	exorbital lachrymal gland	1	1	1	1	-	1
	intra-orbital lachrymal gland	1	1	1	1	-	1
	Harderian gland	1	1	1	1	-	1
	salivary glands	1	1	1	1	-	1
Gastro-intestinal	caecal contents	1	2	1	1	-	1
	small intestine contents	3	3	1	1	1	1
	small intestine mucosa	1	1	-	-	-	-
	stomach contents	3	3	2	1	1	1
	stomach mucosa	-	-	3	3	2	2
	large intestine contents	1	2	1	1	-	2
	large intestine mucosa	-	1	-	-	-	-
Gonads	epididymides	1	1	1	1	-	-
	prostate	1	1	1	-	-	1
	seminal vesicles	1	1	1	1	-	1
	testis	1	1	1	1	-	1
Muscular	myocardium	1	1	1	1	1	1
	skeletal muscle	1	1	1	1	1	1
	tongue	1	1	1	1	1	1
Urinary	kidney	3	2	2	2	2	2
	bladder	3	2	2	1	-	1
Others	blood	2	2	1	1	1	1
	bone marrow	1	1	1	1	-	-
	brown fat	2	2	2	2	2	2
	fur	2	2	2	2	2	2
	lens	1	1	1	1	1	1
	liver	3	3	3	2	2	2
	lung	2	2	1	1	1	1
	nasal mucosa	3	3	3	3	3	3
	pancreas	1	1	1	1	-	1
	spleen	1	1	1	1	-	1
	tooth pulp	1	1	1	1	-	-

Scoring code: 3. Concentrations described as "highest" in text
2. Concentrations described as "lower" in text
1. Concentrations described as "lowest" in text

N.B. Scores may be compared at any one sacrifice time, but not necessarily across times

The data in this table have been checked for accuracy by the reviewer.

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Radioactive Components in Urine

Enzymatic hydrolysis of urine from rats that received 10 mg/kg caused no discernible effect in metabolic pattern, seen after TLC development. This indicates that no cleavable sulphate or glucuronide was present in urine from rats that had received a single 10 mg/kg dose (see Table 50 below, taken from the applicant's report).

TABLE 50

Proportions of radioactive components in the urine of rats after single oral doses of ^{14}C-dazomet at a dose level of 10 mg/kg
tlc solvent system: chloroform:methanol:water:formic acid (75:25:3:3, by volume)

Results are expressed as % dose*

Approximate R_f	0 - 8 hour				8 - 24 hour			
	Male		Female		Male		Female	
	Untreated	Enzyme-treated	Untreated	Enzyme-treated	Untreated	Enzyme-treated	Untreated	Enzyme-treated
0.04 (M1)	4.2	3.7	3.4	2.9	2.9	2.4	3.1	3.2
0.13 (M2)	3.9	3.6	2.6	2.8	2.7	2.5	3.1	3.0
0.24 (M3)	2.8	2.9	2.0	1.7	1.6	1.3	2.2	2.4
0.42 (M4)	5.8	5.6	4.4	4.2	7.4	7.2	7.5	7.9
0.50 (M5)	20.3	21.3	19.5	20.4	7.2	7.8	11.2	10.4
Others	2.6	2.5	1.6	1.5	1.4	1.4	2.3	2.4

* Calculated as $\frac{\text{mean \% dose/stated time} \times \text{proportion (\%)}}{100}$

The data in this table has been checked for accuracy by the reviewer.

As seen from Table 1 (page 8), around 22 percent of the dose was excreted via the lungs, most of it as CO_2. The two urinary metabolites with R_f 0.50 and 0.42 correspond to around 30 and 13 percent of dose, respectively, during the 0 to 24 hour period and a third one with R_f 0.24 constituted 4 to 5.5 percent of dose. None of the metabolites in urine corresponded to unchanged dazomet. It was concluded that dazomet had undergone extensive biotransformation.

A similar metabolic pattern was seen for urine collected from 100 mg/kg treated rats but the proportions of components identified in urine and gasses expired differed. In the urine from rats treated for 15 consecutive days with dazomet at 10 mg/kg/day, the components were the same and the proportion of components in the urine and expired air were similar to that seen for the single 10 mg/kg dose. Tables for these two studies are not shown in this review.

Proportions of Radioactive Components in Bile

Components in both the urine and bile from the same biliary duct cannulated rats are shown in Table 56, taken from the applicant's report.

TABLE 56

Proportions of radioactive components in the urine and bile of rats with cannulated bile ducts after single oral doses of ^{14}C-dazomet at a dose level of 10 mg/kg tlc solvent system: chloroform:methanol:water:formic acid (75:25:3:3, by volume)

Results are expressed as % dose*

Approximate Rf	0 - 24 hour urine				0 - 24 hour bile			
	Male		Female		Male		Female	
	Untreated	Enzyme-treated	Untreated	Enzyme-treated	Untreated	Enzyme-treated	Untreated	Enzyme-treated
0.04 (M1)	9.5	7.6	3.9	3.9	2.0	2.1	1.7	1.6
0.13 (M2)	6.7	6.5	4.2	4.0	2.2	1.7	1.4	1.2
0.24 (M3)	5.1	5.6	4.2	4.5	-	-	-	-
0.34 (M7)	-	-	-	-	1.3	1.5	1.1	1.1
0.39 (M6)	1.8	1.2	-	-	-	-	-	-
0.42 (M4)	6.8	8.0	6.1	6.3	-	-	-	-
0.50 (M5)	14.8	15.9	28.0	27.5	-	-	-	-
0.59 (M8)	-	-	-	-	0.9	1.0	0.7	0.8
Others	4.8	4.5	3.7	3.9	1.7	1.6	1.2	1.3

* Calculated as $\frac{\text{mean \% dose/stated time x proportion (\%)}}{100}$

The data in this table has been checked for accuracy by the reviewer.

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Components found in urine of cannulated rats were similar to that in intact rats. The metabolic pattern in bile was quite different from that seen in urine. For example, the chief components in urine with R_f 0.50, 0.42, and 0.24 were not observed in bile. Important components in bile with R_f 0.34 and 0.59 were not identified in urine. However, with the 100 mg/kg dose, the component with R_f of 0.42 was observed in bile (Table 58 of the submitted report, which is not shown in this review). In all other respects, the same components seen in bile from rats receiving 100 mg/kg were the same as that seen for 10 mg/kg.

Components in Methanol Extracts of Tissues

Liver and kidneys from rats that had received 100 mg/kg and killed 0.5 hour after dosing were used.

TABLE 59

Proportions of radioactive components in the methanol extracts of liver and kidneys from rats sacrificed 0.5 hours after single oral doses of ^{14}C-dazomet at a dose level of 100 mg/kg

tlc solvent system:chloroform:methanol:water:formic acid (75:25:3:3, by volume)

Results are expressed as % applied radioactivity and % tissue radioactivity

Approximate R_f	Male				Female			
	Liver		Kidneys		Liver		Kidneys	
	% applied	% tissue	% applied	% tissue	% applied	% tissue	% applied	% tissue
0.04 (M1)	30.2	20.2	18.5	15.5	13.3	11.6	11.9	8.9
0.13 (M2)	11.9	8.0	54.2	45.5	21.0	18.3	58.1	43.6
0.50 (M5)	25.4	17.0	4.1	3.4	12.2	10.6	5.1	3.8
0.90 (M9)	25.8	17.3	4.8	4.0	47.2	41.1	5.4	4.1
Others	6.7	4.5	18.4	15.5	6.3	5.5	19.5	14.6

The data in this table has been checked for accuracy by the reviewer.

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Components found in tissues of both organs were the same but the proportions were different. An additional component with an R_f of 0.9 was present at substantial levels in both tissues, particularly in livers, and had not been previously detected in urine or bile. It was claimed that this had a similar R_f as dazomet but it was not unchanged dazomet. Components with R_f 0.42 and 0.24, both of which were consistently seen in urine, were not identified in liver or kidneys.

Identification of Metabolites in Urine

Metabolites were identified after purification by means of TLC and HPLC, by means of their electron impact and chemical ionization mass spectra and comparisons to laboratory synthesized compounds.

The component with an R_f of 0.5, the chief urinary metabolite, also found in bile and tissues of liver and kidney, showed an electron impact mass peak due to:

$$Me\ N\ CS^+$$

and chemical ionization spectra identical to the N-acetylcysteine conjugate of:

$$Me\ N\ CS{+}H^+;\ \text{methyl isothiocyanate}$$

and

$$H\ S\ CH_2.CH(COOH)NH\ CO\ CH_3 + H^+$$

These were confirmed by FAB mass spectra and identical R_f's to synthetic compounds.

The metabolite with R_f 0.42 had similar mass spectra to that with R_f 0.50 and had an R_f identical to synthetic glycine conjugate of Me N CS but different mass spectra; therefore not unequivocally identified. A tentative structure, indicated as M4, is shown in the scheme on page 3.

The urinary metabolite with R_f 0.13, also found in bile and as a major component in both liver and kidneys, also co-chromatographed with the synthetic glycine conjugate of Me N CS but was not isolated in sufficient quantities from urine for further studies.

Part II. The Biokinetics and Metabolism of ^{14}C-Metam Sodium in the Rat

Specific activities of preparations used were:

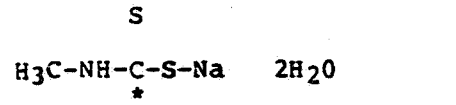
Pure radiochemical metam sodium: 64.5 uCi/mg
Dosage with 10 mg/kg: 15,520 dpm/ug
Dosage with 100 mg/kg: 2227 dpm/ug

Purity of ^{14}C-metam sodium: > 99 percent (Batch 216/5/1)

Purity of nonlabeled compound: 99 percent (Batch CH 686001)

Impurities in the preparation are not given.

Chemical Structure:



Sodium N-methyldithiocarbamate

Molecular Weight: 165.21

Stability of pure compound was not specified. Stability and homogeneity studies with dosage forms in aqueous carboxymethylcellulose were not found.

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Materials and Methods

These were identical to those for dazomet in Part I, except as may be indicated below. However, only single dose, no multiple dose or biliary excretion studies were performed.

Excretion-Retention Study

A summary of excretion-tissue retention from 0 to 168 hours was as follows:

TABLE 1

Mean excretion and retention of radioactivity by male and female rats after single oral doses of ^{14}C-metam sodium at dose levels of 10 and 100 mg/kg

Results are expressed as % dose

Dose level	10 mg/kg		100 mg/kg	
	♂	♀	♂	♀
Tissues	2.01	1.75	1.17	1.32
Urine (0-168 hours)	52.02	58.09	37.34	42.42
Cage washings	0.10	0.05	0.06	0.04
Faeces (0-168 hours)	4.48	2.88	1.87	1.57
Expired air trap 1 (0-72 hours)	0.45	1.26	24.53	24.04
Expired air trap 2 (0-72 hours)	19.56	18.13	7.20	5.53
Expired air trap 3 (0-72 hours)	18.35	13.80	21.34	17.63
Total recovery	96.96	95.95	93.50	92.55

The data in this table has been checked for accuracy by the reviewer.

Table 1 from the applicant's report shows that the chief route of excretion was via the urine with recovery of 52 or 58 percent of dose in males or females after 168 hours at low dose and only 37.3 or 42.4 percent of dose at high dose. Total recoveries in feces after 7 days were about 4.5 or 3 percent of dose in males or females, which appeared to be somewhat reduced at the high dose. Radioactivity found in expired air by 72 hours in trap 1, which is methyl isothiocyanate, was only about 0.5 or 1.3 percent of dose at low dose but rose to around 24 percent of dose with the 100 mg/kg dose. Total excreted as CO_2 (air trap 2) was decreased from 18 to 19 percent to only 5.5 to 7.2 percent of dose at the 100 mg/kg dose. However, excretion as COS and/or

CS_2 (trap 3) may have been slightly decreased when expressed as percentage of dose. Tissue retention amounted to 1.75 or 2 percent of dose with the 10 mg/kg dose and was slightly reduced at the higher dose. Total excretion (total recovered minus tissue retention by 168 hours) amounted to about 91 to 95 percent.

Table 2, which follows, also taken from the applicant's report, shows the excretion pattern by the time collection periods for urine, feces, and expired air.

TABLE 2

Mean excretion of radioactivity in the urine, faeces and expired air of male and female rats after single oral doses of ^{14}C-metam sodium at dose levels of 10 and 100 mg/kg

Results are expressed as % dose

Dose level	10 mg/kg		100 mg/kg	
	♂	♀	♂	♀
Urine				
0 - 8	24.19	26.04	17.83	19.17
8 - 24	22.30	27.30	16.00	19.17
24 - 48	2.97	2.66	2.18	2.73
48 - 72	1.12	0.88	0.64	0.62
72 - 96	0.52	0.45	0.25	0.26
96 - 120	0.39	0.31	0.18	0.17
120 - 144	0.31	0.24	0.14	0.14
144 - 168	0.22	0.21	0.12	0.16
Faeces				
0 - 24	2.98	0.83	0.96	0.66
24 - 48	1.03	1.59	0.67	0.63
48 - 72	0.25	0.22	0.13	0.18
72 - 96	0.08	0.12	0.04	0.04
96 - 120	0.05	0.06	0.04	0.03
120 - 144	0.04	0.04	0.02	0.02
144 - 168	0.03	0.03	0.02	0.02
Expired air trap 1				
0 - 24	0.37	1.12	23.91	23.39
24 - 48	0.06	0.10	0.57	0.57
48 - 72	0.03	0.03	0.06	0.08
Expired air trap 2				
0 - 24	18.44	17.03	6.68	5.00
24 - 48	0.88	0.87	0.40	0.43
48 - 72	0.24	0.23	0.11	0.11
Expired air trap 3				
0 - 24	17.99	13.55	20.41	17.00
24 - 48	0.35	0.25	0.82	0.57
48 - 72	0.01	<0.02	0.11	0.06

The data in this table has been checked for accuracy by the reviewer.

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Total recoveries by 24 hours in urine, feces, and expired air combined amounted to 84.4 tc 96.3 percent of dose with both the 10 and 100 mg/kg doses.

Organ distribution of radioactivity observed 168 hours after dosing, expressed as ug metam sodium per gram of tissue, is shown in Table 3, taken from the applicant's report.

TABLE 3

Mean concentrations of radioactivity in the tissues of male and female rats sacrificed at 168 hours after single oral doses of ^{14}C-metam sodium at dose levels of 10 and 100 mg/kg

Results are expressed as µg/g

Dose level	10 mg/kg		100 mg/kg	
	♂	♀	♂	♀
Eyes	0.077	0.084	0.48	0.51
Brain	0.071	0.086	0.46	0.61
Adrenal glands	0.210	0.225	1.58	1.78
Bone marrow	0.090	0.156	0.42	0.71
Thyroid gland	1.28	3.09	6.24	7.55
Muscle	0.082	0.089	0.45	0.54
Fat	0.076	0.040	0.32	0.27
Pancreas	0.077	0.116	0.53	0.66
Lungs	0.323	0.924	1.50	3.46
Ovaries	-	0.340	-	2.12
Testes	0.036	-	0.25	-
Uterus	-	0.118	-	0.59
Spleen	0.067	0.125	0.62	0.93
Kidneys	0.734	1.29	3.49	6.59
G.I. tract	0.060	0.098	0.30	0.42
Liver	0.765	0.245	3.58	1.20
Whole-blood	0.219	0.263	2.04	3.01
Plasma	0.044	0.072	0.23	0.33
Heart	0.168	0.247	0.95	1.23
Carcass	0.146	0.172	1.05	1.53

G.I. tract Gastro-intestinal tract

The data in this table has been checked for accuracy by the reviewer.

Highest uptake in both sexes was by the thyroid at both dose levels. High uptake was also seen by kidneys, liver, and lungs, all three considered as organs of excretion. Next highest uptake were by whole blood, adrenals, and ovaries. Concentrations in all organs, except liver and possibly fat, were consistently higher in females than in males.

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Concentrations in Plasma

Five of each sex received 10 and 100 mg/kg and blood samples were taken from the tail vein at the time intervals listed in Table 16 from the applicant's report, which follows.

TABLE 16

Mean concentrations of radioactivity in the plasma of rats after oral doses of ^{14}C-metam sodium at dose levels of 10 and 100 mg/kg

Results are expressed as µg/ml

Time (hours)	10 mg/kg		100 mg/kg	
	♂	♀	♂	♀
Pre-dose	<0.019	<0.019	<0.13	<0.13
0.25	1.08	1.19	10.6	11.2
0.5	1.50	1.68	10.4	8.09
1	1.57	1.84	11.0	11.2
2	1.19	1.61	11.0	9.87
3	0.979	1.33	7.23	9.48
4	0.845	1.06	6.29	9.22
6	0.776	0.884	6.04	8.70
24	0.334	0.440	2.96	5.42
48	0.197	0.283	1.49	2.65
72	0.139	0.226	0.93	1.59
96	0.102	0.166	0.66	1.18
120	0.074	0.126	0.51	0.83
168	0.043	0.081	0.28	0.49
240	0.022	0.049	0.15	0.26

The data in this table has been checked for accuracy by the reviewer.

T_{max} in plasma for males and females at low dose was 1 hour. At high dose T_{max} occurred over a period of 0.25 to 1 hour. Plasma levels were consistently higher for females than for males at all time periods.

The following is a summary of pharmacokinetic data derived from the plasma levels, extracted from Tables 17 to 20 of the applicant's report.

Dosage	10 mg/kg				100 mg/kg			
Sex	Males		Females		Males		Females	
Parameter	Mean	SD	Mean	SD	Mean	SD	Mean	SD
T1	72.00	0.00	76.80	10.73	72.00	0.00	72.00	0.00
T1	225.60	32.20	225.60	32.20	225.60	32.20	240.00	0.00
T0.5	60.8	5.7	74.1	11.4	61.7	7.1	64.2	2.2
reg	0.995	0.006	0.996	0.001	0.992	0.005	0.992	0.004
AUCO	36.4	1.9	52.2	3.0	277.2	12.9	446.6	67.8

T1 is the entered terminal slope start time (hours).
T2 is the entered terminal slope end time (hours).
T0.5 is the terminal half-life (hours).
reg is the regression coefficient (r) of the fitted line.
AUCO is the area under the normal curve without extrapolation (ug/mL.hours).

The increase in dose from 10 to 100 mg/kg had no apparent effects on terminal slope start and end times or on terminal half-lives. Terminal half-lives were about 61 and 74 hours for males and females at low dose, 62 and 64 hours at high dose. AUC's were higher for females at both dose levels.

Proportions of Radioactive Components in Urine

Results after TLC development are shown in in Tables 22 (10 mg/kg dose) and 24 (100 mg/kg dose) taken from the applicant's report, expressed as percent of dose.

TABLE 22

Proportions of radioactive components in the urine of rats after oral doses of ^{14}C-metam sodium at a dose level of 10 mg/kg

Tlc system: chloroform : methanol : water : formic acid (75 : 25 : 3 : 3, by volume)

Results are expressed as (%) dose

Approx. R_f (component)	0 - 8				8 - 24			
	Male		Female		Male		Female	
	Untreated	Enzyme-treated	Untreated	Enzyme-treated	Untreated	Enzyme-treated	Untreated	Enzyme-treated
0.04 (M1)	3.1	3.0	3.4	3.4	3.5	3.3	3.6	1.8
0.13 (M2)	2.5	2.4	2.4	3.0	3.0	2.8	2.5	2.0
0.24 (M3)	1.3	2.0	1.2	1.5	1.9	2.2	1.2	1.5
0.42 (M4)	3.5	2.8	2.5	2.3	4.7	4.9	2.6	6.6
0.50 (M5)	9.9	10.1	13.3	12.5	6.2	5.9	13.9	12.6
Others	3.8	3.9	3.3	3.3	3.1	3.3	3.4	2.9

The data in this table has been checked for accuracy by the reviewer.

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TABLE 24

Proportions of radioactive components in the urine of rats after oral doses of ^{14}C-metam sodium at a dose level of 100 mg/kg

Tlc system: chloroform : methanol : water : formic acid (75 : 25 : 3 : 3, by volume)

Results are expressed as (%) dose

Approx. R_f (component)	0 - 8				8 - 24			
	Male		Female		Male		Female	
	Untreated	Enzyme-treated	Untreated	Enzyme-treated	Untreated	Enzyme-treated	Untreated	Enzyme-treated
0.04 (M1)	1.2	1.0	1.0	0.9	2.0	1.5	1.5	1.4
0.13 (M2)	1.5	1.4	1.2	1.2	1.8	1.5	1.6	1.5
0.24 (M3)	0.6	0.6	0.4	0.4	0.7	0.6	0.7	0.7
0.42 (M4)	2.1*	2.1*	1.7*	1.6*	3.8	3.6	4.4	3.9
0.50 (M5)	11.5	11.7	13.9	14.1	6.2	7.1	9.4	10.0
Others	1.0	1.0	0.9	1.0	1.6	1.6	1.5	1.7

* M4 radioactivity distributed between 2 components

The data in this table has been checked for accuracy by the reviewer.

Components found were identical to those seen after dazomet administration but the amounts recovered were lower with both doses (see page 18 for comparison). Enzymatic hydrolysis had no discernible effect on the quantitate composition of components, indicating no cleavable sulphate or glucuronide was present, as was found for dazomet.

Proportion of Components in Liver and Kidneys

Organs were obtained 0.5 hour after a 100 mg/kg oral dose. The methanol extracts were subjected to TLC for resolution and quantification of components.

TABLE 25

Proportions of radioactive components in the methanol extracts of liver and kidneys from rats sacrificed 0.5 hours after a single oral dose of ^{14}C-metam sodium at a dose level of 100 mg/kg

Tlc system: chloroform : methanol : water : formic acid (75 : 25 : 3 : 3, by volume)

Results are expressed as proportions (% rad) of the chromatogram and proportions (% tissue) of the tissue radioactivity

Approx. R_f (component)	Male				Female			
	Liver		Kidneys		Liver		Kidneys	
	% rad	% tissue	% rad	% tissue	% rad	% tissue	% rad	% tissue
0.04 (M1)	47.9	31.6	16.0	13.1	30.5	23.2	9.5	6.4
0.13 (M2)	11.6	7.7	54.9	45.0	19.3	14.7	64.4	43.1
0.50 (M5)	18.1	11.9	9.4	7.7	14.2	10.8	7.2	4.8
0.88 (M6)	3.1	2.0	ND	ND	15.9	12.1	ND	ND
Others	19.3	12.7	19.7	16.2	20.1	15.3	18.9	12.7

The data in this table has been checked for accuracy by the reviewer.

Four components were detectable in liver; R_f 0.04, 0.13, 0.50, and 0.88. The first three of these four components were discernible in kidney but the fourth one with R_f 0.88 was probably below the detectable level. The first three components were identical in R_f to that seen in these organ extracts following dazomet administration whereas the fourth component differed slightly; R_f = 0.88 following metam sodium, R_f = 0.90 following dazomet (see page 20 for comparison).

Part III. The Biokinetics and Metabolism of Methyl Isothiocyanate-^{14}C in the Rat

$$H_3C-N=\overset{*}{C}=S$$

MITC

Radiochemical purity of the synthetic compound was 95 percent, by reverse phase HPLC. A single component was seen by GC-MS analysis with a "retention time and mass spectrum identical to authentic."

Specific Activities

Purified MITC: 16.33 uCi/mg
4.4 mg/kg dose: Dissolve 0.79 ug/mL in 1 percent carboxymethylcellulose
33 mg/kg dose: Dissolve 6.6 ug/mL in 1 percent carboxymethylcellulose

Each rat received 5 mL/kg for low dose, 6 mL/kg for high dose.

Nonradiolabeled MITC was obtained from Aldrich Chemical Company in Milwaukee, WI.

Chemical identity and purity were determined by GC-MS to demonstrate a single component, also by HPLC, retention time and mass spectrum with comparisons to authentic compound.

There were no tests performed to demonstrate stability and homogeneity of the dosing preparations.

Materials and Methods

These were basically similar or identical to those described in Part I of this review, unless otherwise indicated below. Only single dose experiments were carried out.

Results

Excretion-Retention Studies

A summary of excretion-tissue retention of MITC over a 168-hour period following 4.4 and 33 mg/kg single doses is shown in Table 1, taken from the applicant's report.

TABLE 1

Mean excretion and retention of radioactivity by male and female rats after single oral doses of methyl isothiocyanate-^{14}C at dose levels of 4.4 and 33 mg/kg

Results are expressed as % dose

Dose level	4.4 mg/kg		33 mg/kg	
	♂	♀	♂	♀
Tissues	2.20	1.86	1.71	2.29
Urine (0 - 168 hours)	84.43	86.36	87.09	85.57
Cage washings	0.15	0.07	0.18	0.15
Faeces (0 - 168 hours)	2.74	1.45	1.93	1.83
Expired air trap 1 (0 - 72 hours)	0.95	1.51	0.72	1.67
Expired air trap 2 (0 - 72 hours)	16.08	14.88	7.32	7.23
Expired air trap 3 (0 - 72 hours)	0.05	0.04	0.43	0.48
Total recovery	106.59	106.16	99.37	99.22

The data in this table has been checked for accuracy by the reviewer.

This shows that 7 days after dosing, about 85 percent of the administered dose was eliminated in urine, the major route of excretion; no difference in percent of dose excreted in urine due to dosage or sex. Only about 1.8 to 2.7 percent of the dose was excreted in feces. With the 4.4 mg/kg dose, about 16.5 to 17 percent of the dose was excreted in air within 72 hours of which 15 to 16 percent of the total dose was excreted as CO_2 (expired air trap 2). The amount excreted in air with the 33 mg/kg dose was reduced to 8.5 to 9.5 percent of the administered dose with about 7.3 percent of the dose excreted as CO_2 within 72 hours. The amounts retained by tissues of the organisms amounted to 1.7 to

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2.3 percent of the dose with no apparent difference due to dosage or sex. Total recoveries were around 1^5 percent for the low dose and about 99 percent for the high dose.

Table 2 which follows, also taken from the applicant's report, shows the excretion pattern by the time collection periods for all three routes of excretion.

TABLE 2

Mean excretion of radioactivity in the urine, faeces and expired air of male and female rats after single oral doses of methyl isothiocyanate-^{14}C at dose levels of 4.4 and 33 mg/kg

Results are expressed as % dose

Dose level	4.4 mg/kg		33 mg/kg	
	♂	♀	♂	♀
Urine				
0 - 8	71.43	73.65	58.76	54.62
8 - 24	9.25	8.80	22.93	25.51
24 - 48	1.83	1.84	2.78	3.33
48 - 72	0.95	0.83	1.11	1.04
72 - 96	0.39	0.40	0.43	0.42
96 - 120	0.26	0.29	0.33	0.27
120 - 144	0.16	0.32	0.43	0.20
144 - 168	0.15	0.22	0.31	0.19
Faeces				
0 - 24	1.99	0.66	1.13	0.93
24 - 48	0.34	0.35	0.47	0.54
48 - 72	0.17	0.19	0.13	0.18
72 - 96	0.09	0.11	0.06	0.06
96 - 120	0.06	0.05	0.05	0.04
120 - 144	0.04	0.05	0.07	0.04
144 - 168	0.04	0.05	0.04	0.04
Expired air trap 1				
0 - 24	0.69	1.24	0.49	1.20
24 - 48	0.16	0.18	0.14	0.30
48 - 72	0.10	0.08	0.09	0.16
Expired air trap 2				
0 - 24	15.24	14.09	6.78	6.53
24 - 48	0.63	0.60	0.40	0.51
48 - 72	0.21	0.18	0.14	0.19
Expired air trap 3				
0 - 24	0.04	0.04	0.29	0.33
24 - 48	<0.02	<0.02	0.08	0.10
48 - 72	0.01	<0.02	0.05	0.04

The data in this table has been checked for accuracy by the reviewer.

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Total excretion by 24 hours in urine, feces, and air combined amounted to 99 percent with the 4.4 mg/kg dose and 89 percent with the 33 mg/kg dose.

Organ distribution of radioactivity, found in animals that were killed 168 hours after dosing, expressed as ug equivalents of ^{14}C-MITC, is shown in Table 3, taken from the applicant's report.

TABLE 3

Mean concentrations of radioactivity in the tissues of male and female rats sacrificed at 168 hours after single oral doses of methyl isothiocyanate-^{14}C at dose levels of 4.4 and 33 mg/kg

Results are expressed as µg equivalents ^{14}C-MITC/g

Dose level	4.4 mg/kg		33 mg/kg	
	♂	♀	♂	♀
Tissues				
Eyes	0.034	0.027	0.29	0.41
Brain	0.024	0.035	0.21	0.29
Adrenal glands	0.058	0.060	0.38	0.81
Bone marrow	0.024	<0.078	<0.24	0.62
Thyroid gland	0.248	0.370	1.58	4.07
Muscle	0.021	0.026	0.15	0.20
Fat	0.012	0.011	0.16	0.12
Pancreas	0.031	0.040	0.22	0.29
Lungs	0.037	0.077	0.41	1.04
Ovaries	-	0.041	-	0.50
Testes	0.010	-	0.08	-
Uterus	-	0.024	-	0.20
Spleen	0.023	0.036	0.20	0.28
Kidneys	0.080	0.137	0.76	1.57
G.I. tract	0.036	0.068	0.25	0,41
Liver	0.119	0.107	0.89	0.65
Whole-blood	0.062	0.094	0.67	0.91
Plasma	0.013	0.028	0.09	0.14
Heart	0.038	0.059	0.30	0.51
Carcass	0.079	0.080	0.55	0.86

The data in this table has been checked for accuracy by the reviewer.

The highest uptake in both sexes was by the thyroid gland with both dose levels. Concentrations in liver, kidneys, lungs, ovaries, whole blood, G.I. tract, and carcass ranged between 5 to 50 percent of that found in thyroid. As with dazomet and metam sodium, there was a tendency for higher tissue levels in organs of females than in males. Concentration in tissues after 168 hours were lower for MITC than for the two other compounds,

but the dosage, based on mg/kg or moles/kg, was lower with both the low and high dose of MITC.

Concentration in Plasma

Five of each sex received 4.4 or 33 mg/kg and blood samples were taken from the tail vein at the time intervals listed in Table 16 from the applicant's report, which follows:

TABLE 16

Mean concentrations of radioactivity in the plasma of rats after oral doses of methyl isothiocyanate-^{14}C at dose levels of 4.4 and 33 mg/kg

Results are expressed as µg/ml

Time (hour)	4.4 mg/kg		33 mg/kg	
	♂	♀	♂	♀
Pre-dose	<0.009	<0.009	<0.08	<0.08
0.25	1.33	1.56	8.47	8.95
0.5	1.53	1.60	10.6	11.4
1	1.14	1.45	9.67	11.4
2	0.599	0.748	6.65	7.93
3	0.428	0.478	4.38	7.26
4	0.313	0.388	3.69	5.00
6	0.233	0.288	2.44	3.28
24	0.143	0.185	1.01	1.18
48	0.094	0.153	0.57	0.73
72	0.063	0.091	0.39	0.59
96	0.047	0.076	0.32	0.38
120	0.039	0.059	0.24	0.28
168	0.022	0.049	0.15	0.18
240	0.012	0.022	0.08	0.09

The data in this table have been checked for accuracy by the reviewer.

T_{max} was at about 0.5 hour in males and females at both doses. Plasma levels were consistently higher for females at all time periods with both doses.

The following is a summary of pharmacokinetic data derived from the plasma level data, extracted from Tables 17 to 20 of the applicant's report.

Dosage	10 mg/kg				100 mg/kg			
Sex	Males		Females		Males		Females	
Parameter	Mean	SD	Mean	SD	Mean	SD	Mean	SD
T1	96.00	0.00	76.80	20.08	76.80	10.73	76.80	20.08
T2	240.00	0.00	240.00	0.00	211.20	39.44	196.80	39.44
T0.5	73.6	4.6	83.7	7.0	72.0	5.3	70.5	8.4
reg	0.988	0.010	0.971	0.034	0.994	0.004	0.992	0.006
AUCO	16.7	2.6	24.2	2.0	123.8	12.4	154.7	27.8

T1 is the entered terminal slope start time (hours).
T2 is the entered terminal slope end time (hours).
T0.5 is the terminal half-life (hours).
reg is the regression coefficient (r) of the fitted line.
AUCO is the area under the normal curve without extrapolation (ug/mL.hours).

The increase in dose from 4.4 to 33 mg/kg had no effects on the plasma terminal slope at start time but may have caused a slight decrease in terminal slope at end time. Terminal half-lives ranged between 60.8 to 74.1 hours, with no apparent difference at either dose level or between sexes. AUC was considerably higher in females than in males at both doses.

Proportion of Radioactive Components in Urine

Results are shown in Tables 22 and 24 which follow, taken from the applicant's report.

TABLE 22

Proportions of radioactive components in the urine of rats after oral doses of methyl isothiocyanate-^{14}C at a dose level of 4.4 mg/kg

TLC system: chloroform : methanol : water : formic acid (75 : 25 : 3 : 3, by volume)

Results are expressed as % dose*

Approx. R_f (component)	0 - 8				8 - 24			
	Male		Female		Male		Female	
	Untreated	Enzyme-treated	Untreated	Enzyme-treated	Untreated	Enzyme-treated	Untreated	Enzyme-treated
0.04 (M1)	1.7	1.5	1.5	1.3	0.4	0.4	0.6	0.5
0.13 (M2)	3.1	3.4	3.1	3.7	1.0	0.8	1.0	1.1
0.24 (M3)	1.8	4.0	1.0	2.2	0.8	0.7	0.7	0.7
0.42 (M4)	6.3	5.1	4.3	4.1	3.0	2.5	2.4	2.3
0.50 (M5)	52.6	52.9	58.8	57.4	2.9	4.0	3.4	3.3
Others	5.9	4.4	5.0	4.9	1.1	0.8	0.7	0.9

* Calculated as $\frac{\% \text{ dose/stated time interval}}{100} \times$ Proportion (%) component in urine

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The data in the tables has below have checked for accuracy by the reviewer.

TABLE 24

Proportions of radioactive components in the urine of rats after oral doses of methyl isothiocyanate-^{14}C at a dose level of 33 mg/kg

TLC system: chloroform : methanol : water : formic acid (75 : 25 : 3 : 3, by volume)

Results are expressed as % dose*

Approx. Rf (component)	0 - 8				8 - 24			
	Male		Female		Male		Female	
	Untreated	Enzyme-treated	Untreated	Enzyme-treated	Untreated	Enzyme-treated	Untreated	Enzyme-treated
0.04 (M1)	-	-	-	-	1.0	1.1	1.3	1.2
0.13 (M2)	2.5	2.3	7.0	7.5	1.7	1.8	3.2	3.4
0.24 (M3)	0.7	1.0	0.8	0.9	1.3	1.5	1.3	1.4
0.42 (M4)	2.1	2.5	1.9	2.3	2.7	3.4	3.8	3.6
0.50 (M5)	51.1	50.2	42.4	42.0	15.1	13.6	15.0	14.9
Others	2.4	2.8	2.6	1.9	1.2	1.4	1.0	1.1

* Calculated as $\frac{\%\ \text{dose/stated time interval}}{100}$ x Proportion (%) component in urine

Patterns and proportions of metabolites were generally similar at low and high dose and the patterns were also similar to those found after oral doses of dazomet and metam sodium, although the proportions of metabolites differed. The most important component, corresponding to over 50 percent of the dose recovered within 24 hours, had an R_f of 0.50. Four other components corresponding to R_f 0.04, 0.13, 0.24, and 0.42 were also separated by TLC. Enzyme treatment had no discernible effect on pattern or proportion of each component.

Proportion of Components in Methanol Extracts of Liver and Kidneys

These organs were obtained from rats that had received a single oral dose of ^{14}C-MITC at 45 mg/kg and killed 0.5 hour after dosing. The results are shown in Table 25, taken from the applicant's report.

TABLE 25

Proportions of radioactive components in the methanol extracts of liver and kidneys from rats after single oral doses of methyl isothiocyanate-^{14}C at a dose level of 45 mg/kg

TLC system: chloroform : methanol : water : formic acid (75 : 25 : 3 : 3, by volume)

Results are expressed as % applied radioactivity and % tissue radioactivity

Approx. Rf (component)	Male				Female			
	Liver		Kidneys		Liver		Kidneys	
	% applied	% tissue	% applied	% tissue	% applied	% tissue	% applied	% tissue
0.04 (M1)	47.1	32.5	77.0	67.0	47.1	31.6	64.9	57.1
0.13 (M2)	12.7	8.8	7.3	6.4	24.1	16.1	24.1	21.2
0.24 (M3)	ND	ND	2.0	1.7	ND	ND	2.4	2.1
0.50 (M5)	26.5	18.3	ND	ND	19.9	13.3	ND	ND
0.88 (M6)	3.2	2.2	ND	ND	1.5	1.0	ND	ND
Others	10.5	7.2	13.7	11.9	7.4	5.0	8.6	7.6

ND Not detected

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0xC977

In liver, the component with R_f of 0.24 was not detectable but this was only a minor component in both the kidneys and urine. Component with an R_f of 0.04 was present in large amounts in both kidneys and liver. A component with an R_f of 0.88 was detected in liver but not in kidneys, nor was it present in urine. The component with an R_f of 0.5, which was present at very high levels in urine and at an appreciable level in liver, was not detectable in the kidneys.

The following table is a summary of excretion and tissue retention of the three substances tested; metam sodium, dazomet and MITC, for the sake of comparisons in the summary and evaluation which follows.

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Summary of Mean Excretion-Retention
After Single Oral Doses

Dose (mg/kg) Mol/kg	Metam Sodium 10 7.7×10^{-5}		Metam Sodium 100 7.7×10^{-4}		Dazomet 10 6.2×10^{-5}		Dazomet 100 6.2×10^{-4}		MITC 4.4 6.0×10^{-5}		MITC 33 4.5×10^{-4}	
Sex	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Urine												
0-8 H	24.2	26.0	17.8	19.2	39.6	33.5	16.7	14.5	71.4	73.7	58.8	54.6
0-24 H	46.5	53.4	34.1	38.3	62.8	62.8	59.4	49.6	80.7	82.5	81.7	80.1
0-168 H	52.0	58.1	37.3	42.4	68.2	68.8	66.5	62.5	84.4	86.4	87.1	85.6
Feces												
0-24 H	3.0	0.8	1.0	0.7	2.4	1.7	0.7	0.7	2.0	0.7	1.1	0.9
0-168 H	4.5	2.9	1.9	1.6	3.3	3.1	2.2	2.3	2.8	1.5	1.9	1.8
Expired Air												
0-24 H												
Trap 1 MITC	0.4	1.1	23.9	23.4	1.0	1.4	1.0	1.6	0.7	1.2	0.5	1.2
Trap 2 CO_2	18.4	17.0	6.7	5.0	16.6	14.6	10.1	8.7	15.2	14.1	6.8	6.5
Trap 3 CS_2, COS	18.0	13.6	20.4	17.0	2.8	5.4	14.3	18.8	0.04	0.04	0.3	0.3
0-72 H												
Trap 1 MITC	0.5	1.3	24.5	24.0	1.1	1.6	1.1	1.7	1.0	1.5	0.7	1.7
Trap 2 CO_2	19.6	18.1	7.2	5.5	17.8	16.0	10.3	9.1	16.1	14.9	7.3	7.2
Trap 3 CS_2, COS	18.4	13.8	21.3	17.6	2.9	5.5	14.8	19.5	0.04	0.04	0.4	0.5
Tissues (168)	2.0	1.8	2.2	1.3	2.7	2.3	2.2	2.4	2.2	1.9	1.8	2.3
Total Recovery	97.0	96.0	93.5	92.6	96.1	97.3	98.9	100.0	106.6	106.1	99.4	99.2
Total Excreted												
By 24 hours	86.3	85.9	86.1	84.4	85.6	85.9	85.5	79.4	98.6	98.5	90.4	89.0
168 hours	95.0	94.2	92.2	91.1	93.3	95.0	94.9	95.1	104.3	104.3	97.4	96.8

Results are expressed as percent of dose.

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Summary and Evaluation

Data from pharmacokinetic and metabolism studies were submitted for three separate compounds; dazomet, metam sodium, and methyl isothiocyanate.(MITC). It was claimed that each of these three compounds were tested at a low- or no-effect level and at a high- or "toxic-effect level," as determined from previous subacute or chronic studies. The levels selected for testing were 10 and 100 mg/kg for the first two compounds, 4.4 and 33 mg/kg for MITC.

Chemical structures of the three compounds differ considerably, but metam sodium and dazomet both form MITC in the soil. MITC is also a key intermediary in the metabolism of both metam sodium and dazomet in the rat (see scheme on page 3). In field studies to determine residues of metam sodium applied to crops, the compound is known to be rapidly and extensively converted to MITC. Therefore, plant samples are often monitored for MITC following application of metam sodium to crops.

The data from tests with all three compounds were submitted to support the application for metam sodium. All three compounds were tested for excretion, retention, tissue distribution and metabolism following a single low and high dose. All three were tested for plasma levels at multiple time periods after dosing. All 3 were tested for distribution of metabolic components in urine after a low and high dose, and in liver and kidneys following a high dose. However, only dazomet was also tested for biliary excretion and metabolic components in bile, collected from bile duct cannulated rats. Only dazomet was tested following 14 daily oral low doses of non-radiactive compound and radioactive compound on day 15, for excretion, retention, and pattern of metabolites in urine. Only dazomet was tested for plasma level determinations and for organ distribution and release following 7 daily oral low doses with ^{14}C-labelled compound. Autoradiographic studies for qualitative organ distribution and release were performed only for dazomet after a single oral high dose and multiple oral low doses.

For the purpose of comparison, excretion-retention data for all three compounds are shown in the table on page 37. Total urinary recovery after 168 hours for the low dose of metam sodium was about 52 and 58 percent in males and females, respectively, which was reduced to 37 or 42 percent with the high dose. In the expired air, only 0.5 and 1.3 percent was excreted as MITC when the low dose was given, but a correspondingly higher amount, 24.5 or 24.0% was excreted with the high dose. Substantial amounts were excreted as CO_2 and CS_2 or COS, but no effect of dosage was evident. The profile of excretion products seen after dazomet or MITC administration was similar, but there were clearly quantitative differences. Fecal excretion, on the other hand, was low, usually not exceeding 3 percent of the administered dose for all three compounds.

Amounts excreted via expired air within 72 hours of dosing was considerably higher for metam sodium than for the two other compounds. Much of it was primarily due to a higher proportion of MITC and CS_2/COS in expired air after a dose of metam sodium. This was explained by the investigators as being due to the fact that metam sodium is unstable under acid conditions, such as in the stomach. The higher lung excretion of metam sodium was paralelled by a reduction in excretion by the kidneys. Nevertheless, for all three compounds, the chief route of excretion was by the kidneys, accounting for 37 to 58% for metam sodium, 63 to 69% for dazomet and around 85% for MITC over the 168 hour collection period. The respiratory route was also important, sometimes accounting for up to 53% for metam sodium, but up to 26% for dazomet and 17% for MITC, over a 72 hour collection period.

Total recoveries of all three compounds by the three routes of excretion combined exceeded 90 percent for both the high and low dose after 168 hours with about 2 percent remaining in the tissues. Of this, 85 percent or more was excreted within the first 24 hours. When these animals were killed 168 hours after dosing, the organ with highest radioactive content for all 3 compounds was found to be the thyroids. High levels were also found in the liver, kidneys and lower but still high amounts in the lungs. The latter 3 organs are considered to be the organs of excretion or biotransformation. Lowest levels were found in the testes, brain and eyes.

In an experiment with repeated doses of dazomet at 10 mg/kg/day for 15 consecutive days of which only the last dose was radioactive, excretion pattern of the labeled compound was very similar to that observed after a single low dose. Tissue levels of radioactivity were also very similar. When ^{14}C-labelled dazomet was administered for 7 consecutive days and the rats killed between 1 to 240 hours after the last dose, highest levels were seen in most organs at 6 hours. The organ of highest uptake and retention was the thyroid. High levels were seen in the G.I. tract, liver and lungs. Even after 240 hours following the last dose, measurable levels were seen in every organ with the highest amounts present in thyroids, and high levels with about 1/10 as much remaining in the kidneys and lungs. Whole body autoradiography following 7 daily doses of radioactive dazomet generally supported the quantitative results found in this study.

In bile duct cannualted rats, dazomet was found to be excreted in the bile, but this route of excretion was considered to play a minor role in the elimination of this compound. The level of excretion in the feces for all 3 compounds was usually about 1.5 to 3.5 percent of dose within 168 hours.

Plasma concentrations following single oral doses of all 3 compounds were measured at six time intervals between 0.25 and 6 hours after dosing, then at 24 hours, and at 24 hour intervals to 240 hours post dosing. With metam sodium, highest levels in the plasma generally occurred one hour after dosing in both males and

females receiving the 10 mg/kg dose, 0.25 to 1 hour following the high dose. Half-lives after 24 hours were about 61 and 74 hours at low dose, 62 and 64 hours at high dose, for males and females, respectively. For dazomet, time to peak plasma levels and half-lives after 24 hours were about the same. With MITC, peak plasma levels were generally seen at about 0.5 hours after dosing with both the 4.4 and 33 mg/kg levels in males or females. Mean half-lives after 24 hours were 74 and 84 hours with low dose, 72 and 71 hours with high dose, for males and females, respectively.

In all of the organ uptake or retention studies and in all plasma concentation studies, tissue levels in all organs and in the plasma were consistently higher in females than in males for all three compounds. Plasma AUC's were consistently and substantially higher for females than for males. Thus, it seems reasonable to expect greater toxicity by these compounds in female rats.

All 3 compounds appeared to have been rapidly and extensively absorbed from the G.I. tract after dosing, based on: 1). rapid appearance in the plasma within 0.25 hours after dosing, 2). T_{max} of 0.5 to 1 hour, 3). total recoveries of 92 percent or greater in urine, air, feces and tissues within 240 hours. For all three compounds, 85% or more was excreted within the first 24 hours, in spite of half-lives after 24 hours that were long.

All three compounds also displayed a similar profile of organ distribution following dosage. Highest uptake was seen in the thyroids and substantial levels were also seen in liver, kidneys and lungs. The lowest amounts were seen in testes, brain and eyes.

Metabolic components , separated by by TLC, were investigated. The chief component of excretion in urine for all three compounds had an R_f of 0.5. In the first 24 hour collected urine following administration, this metabolite represented 16-25% of dose for metam sodium, 30-38% of dose for dazomet and 56-76% of dose for MITC. A second metabolite with an R_f of 0.42 was formed which represented about 5-10% of dose for all three compounds. Three other minor components were found in urine for all three compounds with R_f values of 0.24, 0.13 and 0.04. Based on incubation with enzymes, there was no evidence for glucuronide or sulphate conjugation. None of the metabolites in urine corresponded to unchanged compound in the studies with dazomet. This indicated that dazomet, probably also metam sodium and MITC, had undergone extensive biotransformation.

The major metabolite in urine with the R_f of 0.5 was identified as N-acetyl-S-(N-methylthiocarbamoyl)-L-cysteine. This was considered to represent an adduct of MITC with glutathione followed by N-acetylation. Structure for the metabolite with the R_f of 0.13 (M2) and the tentative structure for R_f 0.42 (M4) are shown in the scheme on page 3 of this review. Both of these compounds are also considered to be conjugation products of MITC with cysteine.

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Metabolic components detected in bile following dazomet administration differed to some extent from those found in urine. For example, components with R_f values of 0.50, 0.42 and 0.24, observed in urine, were not detected in bile. Components with R_f 0.13 and 0.04 were observable in bile and urine. Components with R_f of 0.59 and 0.34 were detected only in bile.

Qualitatively similar patterns of metabolites were usually found in both liver and kidneys following oral dosage with any of the 3 compounds, but they differed to some extent from those found in urine or bile. The metabolite with R_f 0.50, the most important urinary excretion product for all 3 compounds, was found in both organs following dosage with any of the 3 compounds. Component with R_f 0.42, detected in urine, was detected in liver and kidneys of rats given metam sodium or MITC but not dazomet. Components with R_f 0.13 and 0.04, observed in urine, were also seen in both organs with all 3 compounds.

On the basis of these data, the applicant has concluded that metam sodium and dazomet "exhibit an extremely similar kinetic and metabolic profile in the rat." When compared to the data for MITC, it is assumed that MITC is produced in the metabolism of both metam sodium and dazomet. On this basis, the applicant feels justified in a decision to forgo additional studies with metam sodium.

We agree with the applicant that the studies with dazomet and MITC support the pharmacokinetic and metabolism data for metam sodium. There are evidently similarities in absorption from the G.I. tract, products of metabolism, excretion, organ distribution and retention of all three compounds. The data appear convincing that both dazomet and metam sodium are converted to MITC in the early stages of metabolism within rats. Metabolic profiles detected in urine, liver and kidneys were basically qualitatively similar for the three compounds, but there were some differences, mainly quantitative in nature.