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

008736

OCT 23 1991

OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Tetrahydro-3,5-dimethyl-2H-1,3,5-thiadiazine-2-thione (Dazomet): Review of Toxicology Data Submitted by the Registrant.

Caswell No: 840
HED Project Nos: 1-1669; 1-1900; 1-1996; 1-2243
MRID Nos: 418655-01; 418655-02; 418654-01; 418650-01; 418651-01; 418653-01; 419677-01; 920289-11

FROM: Timothy F. McMahon, Ph.D., Toxicologist 10/18/91
Review Section I, Toxicology Branch II
Health Effects Division (H7509C)

TO: Betty Cromptom/ PM Team 51
Registration Division (H7505C)

THRU: Yiannakis M. Ioannou, Ph.D., Section Head
Review Section I, Toxicology Branch II
Health Effects Division (H7509C)

J. M. Ioannou 10/17/91

and

Marcia Van Gemert, Ph.D., Branch Chief
Toxicology Branch II
Health Effects Division (H7509C)

m. van gemert 10/17/91

Registrant: BASF Corporation

Action Requested: Review of the following Toxicology Studies with Tetrahydro-3,5-dimethyl-2H-1,3,5-thiadiazine-2-thione (Dazomet):

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§ 82-1(a) Subchronic Oral Toxicity in Rats
§ 82-1(b) Subchronic Oral Toxicity in Dogs
§ 83-1(a) Chronic Oral Toxicity in Rats
§ 83-1(b) Chronic Oral Toxicity in Dogs
§ 83-2(a) Carcinogenicity in Rats
§ 83-2(b) Carcinogenicity in Mice
§ 83-3 Developmental Toxicity in Rabbits
§ 83-4 Reproductive Toxicity in Rats

I. Data Summary

Subchronic Oral Toxicity in Rats MRID # 418655-02

Dazomet was administered to male and female Wistar rats at nominal dose levels of 0ppm, 20ppm (30 ppm achieved intake in males [1.5 mg/kg/day]; 34 ppm achieved intake in females [1.7 mg/kg/day]) 60ppm (90 ppm achieved intake in males [4.5 mg/kg/day]; 106 ppm achieved intake in females [5.3 mg/kg/day]), 180ppm (274 ppm achieved intake in males [13.7 mg/kg/day]; 308 ppm achieved intake in females [15.4 mg/kg/day]) and 360 ppm (560 ppm achieved intake in males [28.0 mg/kg/day]; 640 ppm achieved intake in females [32 mg/kg/day]). Decreased absolute body weight and body weight gain were observed in male and female rats at the 360 ppm dose level. Statistically significant decreases in serum total protein and albumin were observed at the 60 ppm, 180 ppm, and 360 ppm dose level in male and female rats, but was apparently treatment related only in female rats. Increased absolute liver weight and liver:body weight ratio was observed in male rats from the 60, 180, and 360 ppm dose levels. Increased liver:body weight ratio was observed in female rats at the 180 and 360 ppm dose levels.

Based upon the results of this study, the systemic NOEL is = 20 ppm, and the systemic LEL is = 60 ppm for male rats (increased liver weight, liver:body weight ratio) and LEL=180 ppm for female rats (increased liver:body weight ratio).

The Maximum Tolerated Dose (MTD) appears to have been achieved at 360ppm dazomet (decrease in body weight gain in male and female rats).

Classification: core minimum

Subchronic Oral Toxicity in Dogs MRID # 418655-01

Dazomet was administered to male and female beagle dogs at dose levels of 0 ppm, 25 ppm (0.87 mg/kg/day, males; 0.92 mg/kg/day, females), 100 ppm (3.5 mg/kg/day, males and females), and 400/200 ppm (7.25 mg/kg/day, males; 8.09 mg/kg/day, females). A statistically significant increase in the relative liver: body weight ratio was observed in male and female

dogs from the 400/200 ppm dose level at study termination. Increased hemosiderosis was also observed in the spleen of male and female dogs at the 400/200 ppm dose level. Decreased hemoglobin, erythrocytes, and hematocrit was observed in male and female dogs at the 400/200 ppm dose level on study day 90. There did not appear to be any other toxic effects associated with administration of dazomet.

Systemic NOEL = 100 ppm (males and females).
Systemic LEL = 400/200 ppm (increase in relative liver: body weight ratio; increased hemosiderosis in the spleen of males and females).

Classification: core minimum

Chronic Oral Toxicity in Rats MRID #418654-01

Technical Dazomet was administered to male and female rats in the diet for 104 weeks at doses of 0, 5 ppm (0.23 mg/kg/day males; 0.29 mg/kg/day females), 20 ppm (0.94 mg/kg/day males; 1.19 mg/kg/day females), 80 ppm (3.81 mg/kg/day males; 5.09 mg/kg/day females), and 320 ppm (16.36 mg/kg/day males; 21.54 mg/kg/day females) in order to determine the toxic effects from chronic administration of this chemical. Reduced group mean body weight and body weight gain was observed in male and female rats at the 320 ppm dose level. Significant decreases in hematologic parameters (red blood cells, hemoglobin, hematocrit) were observed in female rats at the 80 and 320 ppm dose level, as were significant decreases in serum albumin, total protein, and globulins, and a significant increase in platelets at 80 and 320 ppm dazomet. Male rats showed slight increases in platelets at the 320 ppm dose level and a significant increase in serum cholesterol at the 80 and 320 ppm dose levels. Relative liver : body weight was also increased in male rats at the 320 ppm dose level, but no significant organ weight increases were observed in female rats.

The No Observed Effect Level (NOEL) = 20 ppm

The Lowest Observed Effect Level (LEL) = 80 ppm (decrease in serum albumin, globulins, total protein, hemoglobin, hematocrit, and red blood cells in female rats; increased serum cholesterol in male rats).

Classification: core guideline

Chronic Oral Toxicity in Dogs MRID # 419677-01

Dazomet was administered to male and female beagle dogs at dose levels of 0, 15ppm (0.28 mg/kg/day, males; 0.35 mg/kg/day, females), 50ppm (1.05 mg/kg/day, males; 1.12 mg/kg/day, females), and 150ppm (3.15 mg/kg/day, males; 3.50 mg/kg/day, females). Toxicity in female dogs was evident at 50 and 150ppm dazomet, and included increased liver : body weight ratio, increased serum alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase activities, discoloration of the liver parenchyma, increased severity of iron positive pigment deposition in the liver, and chronic active hepatitis. Toxicity in male dogs

was limited to one dog at the 150ppm dose level, who showed similar signs as those mentioned above for female dogs.

Systemic NOEL = 15 ppm (females); = 50 ppm (males)
Systemic LEL = 50 ppm (females; increased liver : body weight ratio)
= 150 ppm (males; decreased body weight gain; hematological effects)

Classification: core minimum

Carcinogenicity in Rats MRID #418650-01

Technical Dazomet was administered to male and female rats in the diet for 104 weeks at doses of 0 ppm, 5 ppm (0.2 mg/kg/day males; 0.3 mg/kg/day females), 20 ppm (0.9 mg/kg/day males; 0.84 mg/kg/day females), and 80 ppm (3.71 mg/kg/day males; 4.83 mg/kg/day females). There was no apparent systemic toxicity in either sex at any dose level used in this study. In male and female rats, there was a non-statistically significant increase in malignant lymphoma at 80 ppm test article, while in female rats, there was a non-statistically significant increase in mammary fibroadenoma and adenocarcinoma at 80 ppm. Non-neoplastic lesions in the form of hepatocellular fat deposition and vacuolation (male rats) and mixed cell and basophilic cell foci (female rats) were increased at the 80 ppm dose level.

There is no evidence contained in this study which supports the conclusion that the Maximum Tolerated Dose (MTD) was achieved. In a subchronic toxicity study in rats (MRID # 418655-02), the MTD appeared to have been reached at 360 ppm, the highest dose used in this study. However, the highest dose in the present study (80 ppm) does not approximate the highest dose used in the subchronic study. Thus, the high dose tested in this study was not considered to be adequate to assess the carcinogenic potential of dazomet.

The Systemic Toxicity No Observed Effect Level (NOEL) = 20 ppm

The Systemic Toxicity Lowest Observed Effect Level (LEL) = 80 ppm (increased incidence of neoplastic and non-neoplastic pathology, males and females)

The Maximum Tolerated Dose (MTD)- not achieved

Classification: core supplementary

Carcinogenicity in Mice MRID #418651-01

Technical dazomet was administered to male and female B6C3F1 mice in the diet for 78 weeks at doses of 0 ppm, 20 ppm (3.9 mg/kg/day in males, 5.7 mg/kg/day in females), 80 ppm (15.6 mg/kg/day in males, 21.4 mg/kg/day in females), and 320 ppm (69.9 mg/kg/day in males, 95.0 mg/kg/day in females). Decreased body weight, body weight gain, and food efficiency were observed in male mice from the 320 ppm dose group. Increased liver weight

and liver : body weight ratio was observed in male and female mice from the 320 ppm dose group sacrificed at 52 and 78 weeks. Incidence of hepatocellular adenoma was increased in male and female mice from the 320 ppm dose group, and in male mice from the 80 ppm dose group. A statistically significant trend for increased hepatocellular adenoma and basophilic foci of cellular alteration in the liver was reported in female mice.

Based on the effect of test article on body weight gain in male mice, liver weight in male and female mice, and incidence of basophilic foci of cellular alteration in male and female mice during weeks 0-78 of the study, it appears that the MTD was achieved for dazomet.

The data in this study support the conclusion of limited evidence of carcinogenicity for technical Dazomet, based upon the occurrence of increased incidence of hepatocellular adenomas in male and female mice at 320 ppm dazomet.

The Systemic No Observed Effect Level (NOEL) = 20 ppm

The Lowest Observed Effect Level (LEL) = 80 ppm (increased liver masses in male mice at 78 weeks; increased liver weight in female mice at 78 weeks).

The Maximum Tolerated Dose (MTD) = 320 ppm (decreased body weight gain in male mice during weeks 0-13; increased liver weight and lipid deposition in male and female mice at 78 weeks; increased incidence of basophilic foci of cellular alteration in males and females at 78 weeks).

Classification: core minimum

Developmental Toxicity in Rabbits MRID # 920280-11

Administration of Dazomet technical to pregnant female American Dutch rabbits resulted in maternal toxicity at 25, 50 and 75 mg/kg/day. There was evidence of developmental toxicity of dazomet at the dose levels tested, but insufficient evidence was presented to conclusively demonstrate developmental toxicity.

Maternal NOEL= 12.5 mg/kg/day
Maternal LOEL= 25 mg/kg/day (increased resorptions, resorptions/dam, and decreased body weight gain on days 0-20 [study #2).

Tentative Developmental Toxicity NOEL = 12.5 mg/kg/day
Tentative Developmental Toxicity LEL = 25 mg/kg/day (increased resorptions and resorptions/dam)

Classification: core supplementary

Reproductive Toxicity in Rats MRID # 418653-01

The reproductive toxicity of Dazomet was assessed in male and female Wistar rats by administration of dazomet over two-generations at doses of 0 ppm, 5 ppm, 30 ppm, and 180 ppm. Reduced body weight and body weight gain was observed in F_0 females, F1 males, and F1 females at the 30 and 180 ppm dose level. Reduced body weight and body weight gain was also observed in nursing F1 female rats at the 180 ppm dose level. Increased liver : body weight ratios were observed in F_0 male rats and F1 males and females. Reduced activity of alanine aminotransferase activity in male and female F_0 rats at the 180ppm dose level was observed, as was significantly decreased serum albumin in F_0 female rats at the 180 ppm dose level, and significant decreases in serum globulins in F_0 and F1 male rats at the 180 ppm dose level. An increase in the incidence and severity of intracellular hepatic neutral lipids was observed in F_0 and F1 male rats. No significant effects of test article administration were observed on reproductive performance or viability and survival in pups of the F1a, F1b, and F2 generations.

Parental Toxicity NOEL = 5 ppm

Parental Toxicity LEL = 30 ppm (increased incidence and severity of hepatic intracellular neutral lipids in male rats; decreased body weight in F1 male rats)

Reproductive Toxicity NOEL = or > 180ppm

Reproductive Toxicity LEL- not achieved

II. Toxicology Profile for Dazomet (Food Use)

A. Data Requirements:

Data Requirement	Submitted	Satisfied
Dazomet Technical		
81-1 Acute Oral Toxicity	Y	N
81-2 Acute Dermal Toxicity	Y	N
81-3 Acute Inhalation Toxicity	Y	N
81-4 Primary Eye Irritation	Y	N
81-5 Primary Dermal Irritation	Y	N
81-6 Dermal Sensitization	Y	N
81-7 Acute Neurotoxicity-Rat	N	N
82-1 90 Day Feeding Study-Rodent	Y	Y
82-1 90 Day Feeding Study-Nonrodent	Y	Y
82-2 21 Day Dermal	N	N
82-5 Subchronic Neurotoxicity	N	N
83-1 Chronic Toxicity-Rodent	Y	Y
83-1 Chronic Toxicity-Nonrodent	Y	Y
83-2 Carcinogenicity- Rat	Y	N
83-2 Carcinogenicity-Mouse	Y	Y
83-3 Developmental Toxicity Rat	N	N
83-3 Developmental Toxicity Rabbit	Y	N
83-4 Reproductive Toxicity Rat	Y	Y
84-1 Mutagenicity-Gene Mutation	Y	Y
84-1 Mutagenicity-Structural Chromosome Aberrations	Y	Y
84-1 Mutagenicity-Other Genotoxic Effects	Y	Y
85-1 General Metabolism	Y	Y

III. Toxicology Issues

The registrant submitted a rabbit teratology study under FIFRA 6(a)(2) for review. Insufficient information was provided in order for the Agency to conclusively determine the teratogenicity of dazomet, although data provided in the report indicate possible developmental toxicity.

A rat carcinogenicity study submitted by the registrant was graded as core supplementary data, due to the lack of an MTD in this study. No clear evidence of carcinogenicity was found in this study. However, in a mouse carcinogenicity study, an increase in hepatocellular adenomas was observed in both male and female mice, as well as an increase in the incidence of basophilic foci in the liver (males and females), and hyperplastic foci of the pituitary (females only) at the highest dose tested in this study.

In a preliminary dietary administration study in beagle dogs (project # 11D0250/8522), apparent neurotoxicity in the form of unsteady gait and weakness of hindlimbs was observed from capsule administration at 80 and 320 ppm. In study # 87-0456-0001, sporadic vomiting was observed at 400 ppm test article. Based upon these findings, acute and subchronic testing for neurotoxicity of dazomet is requested by the Agency.

The mouse carcinogenicity study was found to be acceptable by the Agency. Based upon the results of this study, which showed increased incidence of hepatocellular adenoma in treated male and female mice as well as increased basophilic foci of cellular alteration in the liver of female mice, dazomet will be presented before the the HED Carcinogenicity Peer Review Committee for evaluation of the carcinogenicity of this chemical.

The rat carcinogenicity study was found to be unacceptable by the Agency, based upon the lack of an MTD and lack of evidence of carcinogenicity. In addition, the highest dose tested in this study (80 ppm) did not approximate the highest dose tested in the rat subchronic toxicity study (360 ppm), making this inadequate for assessment of dazomet carcinogenicity in rats. The registrant is asked to repeat this study with appropriate dose levels which will produce an MTD in rats.

IV. Existing Data Gaps

The following studies contain data gaps which must be satisfied before food use of dazomet is approved:

§ 81-1 Acute Oral Toxicity
§ 81-2 Acute Dermal Toxicity
§ 81-3 Acute Inhalation Toxicity
§ 81-4 Primary Eye Irritation
§ 81-5 Primary Dermal Irritation
§81-6 Dermal Sensitization
§81-7 Acute Neurotoxicity-Rodent

§82-2 21 Day Dermal Toxicity
§82-5 Subchronic Neurotoxicity-Rodent

§83-2 Carcinogenicity-Rat

§83-3 Teratogenicity-Rabbit
§83-3 Teratogenicity-Rat

V. Recommendations

Toxicology Branch II recommends against a food use for dazomet, based upon the outstanding data gaps and toxicology issues pertaining to this chemical as listed in this memorandum.

Reviewed by: Timothy F. McMahon, Ph.D. 10/11/91
Section I, Toxicology Branch II (H7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. 10/15/91
Section I, Toxicology Branch II (H7509C)

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Data Evaluation Report

Study type: Subchronic oral - rats
Guideline: 82-1

EPA ID Numbers: MRID number: 418655-02
Caswell No: 840
HED Project No: 1-1900

Test material: Dazomet

Synonyms: tetrahydro-3,5-dimethyl-2 H-1,3,5-thiadiazine-2-thione

Study number(s): 30C0318/8544

Sponsor: BASF Corporation
Research Triangle Park, NC

Testing Facility: BASF Aktiengesellschaft
Department of Toxicology
W. Germany

Title of report: Report on the Study of the Oral Toxicity of Dazomet in Rats After 3 Month Administration In the Diet

Author(s): Dr. Hellwig

Study Completed: November 1987

Conclusions: Dazomet was administered to male and female Wistar rats at nominal dose levels of 0ppm, 20ppm (30 ppm achieved intake in males [1.5 mg/kg/day]; 34 ppm achieved intake in females [1.7 mg/kg/day]) 60ppm (90 ppm achieved intake in males [4.5 mg/kg/day]; 106 ppm achieved intake in females [5.3 mg/kg/day]), 180ppm (274 ppm achieved intake in males [13.7 mg/kg/day]; 308 ppm achieved intake in females [15.4 mg/kg/day]) and 360ppm (560 ppm achieved intake in males [28.0 mg/kg/day]; 640 ppm achieved intake in females [32 mg/kg/day]). Decreased absolute body weight and body weight gain were observed in male and female rats at the 360ppm dose level. Statistically significant decreases in serum total protein and albumin were observed at the 60ppm, 180ppm, and 360ppm dose level in male and female rats, but was apparently treatment related only in female rats. Increased absolute liver weight and liver:body weight ratio was observed in male rats from the 60, 180, and 360ppm dose levels. Increased

liver:body weight ratio was observed in female rats at the 180 and 360ppm dose levels.

Based upon the results of this study, the systemic NOEL is = 20 ppm, and the systemic LEL is = 60 ppm for male rats (increased liver weight, liver:body weight ratio) and LEL=180ppm for female rats (increased liver:body weight ratio).

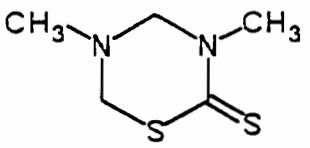
The Maximum Tolerated Dose (MTD) appears to have been achieved at 360ppm dazomet (decrease in body weight gain in male and female rats).

Classification: Core minimum

This study satisfies the guideline requirements (82-1) for a subchronic oral toxicity study in rats.

I. MATERIALS AND METHODS

A. Test Material: Dazomet
purity: > 97%; batch # 26-5297
description: not given in this study; described as a "white powder with a tinge of gray " in MRID# 418655-01.
structure:



B. Vehicle: dietary preparation

C. Test Animals: Species: Wistar rat (Chbb=THOM [SPF]), male and female
Source: Dr. Karl THOMAE, Biberach an der Riss, FRG.
Age: 35 days old at delivery.
Weight (mean): males, 168.8±1.1g; females, 130± 0.86g at start of study. Range: males, 146.8-182.7g; females, 119.6-142.3g

D. Animal Husbandry:
Fifty male and 50 female Wistar rats were used in this study. Animals were allowed 7 days acclimation to the laboratory environment before treatment. Rats were housed individually in type DK III stainless steel wire cages in a temperature (20-24 °C) and humidity (30-70%) controlled room with a 12 hour light/dark cycle. Food (Kliba rats/mice/hamsters maintenance diet "A" 343 meal) and municipal tap water were available ad libitum.
Animals were housed in the same room for the duration of the study. Cages were distributed in such a manner so as to equalize environmental influences. A brief deviation in temperature and humidity control was reported due to technical fault but was not felt to have affected study results.

E. Experimental Design and Dosing:

One day prior to study initiation, rats were randomly distributed to test groups according to weight. Ten rats per sex per dose were used. Test groups included control and the following dose groups:

Group #	Dose (ppm)	Animal #s male	female
1	0	1-10	51-60
2	20	11-20	61-70
3	60	21-30	71-80
4	180	31-40	81-90
5	360	41-50	91-100

Doses for this study were selected based upon data derived from the study of the acute oral toxicity of dazomet in rats, 24 and 30 day feeding studies in rats (project #'s 10C0250/8514, 20C0318/8527) , and a two-year dietary feeding study (Mellon Institute of Industrial Research) [pages 16-17 of registrant report].

F. Dietary Preparation and Analysis:

Dazomet was incorporated into ground diet at the required concentrations by weighing the required amount of test substance and mixing with a small amount of food in a beaker using a spatula. This premix was subsequently prepared in a BOSCH household mixer. Additional amounts of food were then added to the premix to obtain the desired final concentration, and mixing was carried out in a GEBR.LODIGE laboratory mixer for 10 minutes. Test diets were prepared twice a week and stored at 4 °C as soon as possible after mixing.

The registrant stated (page 21 of the report) that stability of the test substance was performed prior to and at the end of the study, but the raw data in support of this were not provided. Stability of dazomet in food was demonstrated to be 1 day at room temperature, and 4 days when kept at 4 °C (page 491 of the report). Homogeneity was analyzed in the low (20ppm) and high (360ppm) dietary mixtures using six samples from each dietary mixture. Results (page 490 of the report) showed acceptable homogeneity (within 6% of nominal).

Concentration of test material at each dietary level was analyzed at the start of the study, after approximately 6 weeks, and again at study termination. Results (pages 492-494 of the report) showed acceptable concentrations of test substance in the diet at each dose level, with the exception of one sample from the 180ppm dose level (page 492), which showed a value 16% below nominal. However, this was not felt to have a significant effect on the study.

Analysis for accuracy of concentration and homogeneity was performed for each concentration on samples taken from six different positions in the mixer. This was done prior to treatment and again on diets prepared for weeks 4, 8, and 13.

G. Statistical Analysis:

According to the registrant (page 35 of the report), statistical analysis of the data was carried out in the Computer Center of BASF Aktiengesellschaft and on the computer systems of the Department of Toxicology.

H. Compliance:

A signed "GLP Statement of Compliance" was provided. This study was conducted in accordance with the OECD principles of Good Laboratory Practice.

A signed statement of "Data Confidentiality Claims" was provided.

A signed "Statement of the Quality Assurance Unit" was provided.

A signed statement of EPA Flagging Criteria was provided.

II. OBSERVATIONS AND RESULTS:

1) **Mortality** : Observations for mortality were made twice daily from Monday-Friday, and once daily on weekends and holidays during the 90 day dosing period.

No mortality was reported during the 90 day test.

2) **Clinical Observations**: Observations for clinical toxicity and pharmacologic effects were made once daily.

No abnormal clinical observations were reported in any dose group of either sex over the course of this study. However, data to which the reviewer was referred in the study (Tables 023-024 in the report) show blood protein concentrations in male and female rats after administration of dazomet, and do not summarize clinical findings.

3) **Body Weight:** Body weight data were collected for all animals immediately prior to study initiation, weekly during the course of the study, and again immediately prior to necropsy. Group mean body weights and body weight gains in male and female rats are summarized in the following Table:

TABLE 1
Group Mean Body Weights in Male and Female Rats from 90 Day Dietary Administration of Dazomet[a]

	Dose Groups									
	males (ppm)					females (ppm)				
Body Weight (g)	0	20	60	180	360	0	20	60	180	360
day 0	169	168	171	169	168	130	131	131	131	131
day 49	349	347	365	351	325	214	218	217	214	192*
day 91	410	407	431	420	379	244	246	245	237	216**
mean weight gain (0-91)	241	239	260	251	211	114	115	114	106	85
% of control	-	99	107	104	87	-	100	100	92	74

Data from Tables 005-012, pages 60-67 of registrant report, N=10
*$p < 0.05$; **$p < 0.01$; vs control by Dunnett's test (two sided).

Body weight and body weight gain were affected in male and female rats at the 360ppm dose level. In male rats, group mean body weight was decreased by 7% on day 49 of the study, and remained so for the duration of the study. Overall body weight gain in the 360ppm dose group of male rats was decreased to 87% of control rats. Male rats at other dose levels were not significantly affected. In female rats, body weight on day 49 of the study was decreased approximately 10% vs the corresponding control value ($p < 0.05$). As in male rats, this decrease in body weight persisted through the end of the study in this dose group. Overall body weight gain was decreased to 74% of control ($p < 0.01$).

4) **Food Consumption:** Individual food consumption data were collected weekly. Food efficiency was also calculated at weekly intervals using the following formula:

$$\frac{BW_{x+n} - BX_x}{FC} \times 100$$

BW_{x+n} = mean body weight on day x+ 7

BW_x = mean body weight on day x

FC = mean food consumption for one week (food consumed from day x-1 to day 1, multiplied by 7.

There did not appear to be significant alterations in food consumption (pages 56-59 of the report) or in food efficiency (pages 68-71 of the report) in either male or female rats over the course of the study.

5) **Intake of Dazomet:** Calculated intake of test material (in mg/kg/day) is summarized in the following Table (Table 2):

Table 2
Group Mean Intake of Dazomet in Male and Female Rats
Administered Dazomet in the Diet for 90 Days[a]

Dose Level (ppm)	Nominal Intake (mg/kg/day)	Achieved Mean Intake (mg/kg/day) males	females
0	0	0	0
20	1.0	1.5(150)[b]	1.7(170)
60	3.0	4.5(150)	5.3(176)
180	9.0	13.7(152)	15.4(171)
360	18.0	28.0(155)	32.0(177)

[a]data from Tables 017-020, pages 17-20 of registrant report
[b]percent of nominal intake

As shown, intake of test material was in the range of 150-177% of nominal across all dose groups. Females rats showed slightly higher intake of test material than male rats. Based upon the observations of test article intake, the dose levels in this study would average 30, 90, 274, and 560 ppm in male rats, and 34, 106, 308, and 640 ppm in female rats. Thus, female rats apparently received a higher dose of test material at all dose levels than male rats in this study.

6) **Ophthalmologic Examination:** Ophthalmic examination was performed in rats from the 0ppm and 360ppm dose groups using a focusable hand-held slit lamp. Examination was performed prior to study initiation and again at study termination. The fundus of rats from these dose groups was examined in addition at the end of the study using a KOWA camera.

There were no apparent ophthalmologic abnormalities as a result of treatment with test article at any dose level (Tables 021-022, pages 76-77 of the report).

7) **Clinical Pathology:**

Blood samples were obtained on days 43 and 86 of the study from the retroorbital venous plexus. (Note: No control samples were obtained). Rats were killed at study termination by carbon dioxide

inhalation followed by exsanguination. Rats were then subjected to gross necropsy and histopathological examination. Tissue samples were preserved in 4% formaldehyde, followed by staining with hematoxylin and eosin (tissues from all rats in the control and high dose groups plus the brain, trachea, liver, kidneys, skeletal muscle, peripheral nerve, and spinal cord from rats in the remaining dose groups). In addition to hematoxylin and eosin stain, liver was stained with oil red O in all rats, and peripheral nerve was stained with bodian and aniline blue in all rats. The liver in some rats was subjected to PAS reaction without nuclear stain and evaluated.

a) Hematology: The following CHECKED parameters were measured:

x total leucocyte count*	- total plasma protein*
x erythrocyte count*	x leukocyte differential*
x hemoglobin*	x mean corpuscular HGB
x hematocrit*	x mean corpusc. HGB conc.
x platelet count	x mean corpusc. volume
x packed cell volume	x prothrombin time
- activated partial thromboplastin time	

Hematological parameters were determined using a Coulter Counter. Differential blood count was determined using an automatic differentiator (HEMATRAK, Munich FRG).

b) Blood Chemistry: The following CHECKED parameters were measured:

x glucose*	x AST(SGPT)*
x albumin*	x ALT(SGOT)*
- globulin (calculated)	x alkaline phosphatase
x creatinine*	- creatine phosphokinase
x total bilirubin*	- lactate dehydrogenase
- direct bilirubin	- sorbitol dehydrogenase
- indirect bilirubin	- gamma glutamyl trans-peptidase
x urea nitrogen*	
x total protein*	
- uric acid	
x calcium*	x triglycerides
x phosphate*	x cholesterol
x sodium*	x chloride*
x potassium*	

*EPA guideline requirement "-" not examined

A summary of relevant alterations in hematology and clinical chemistry follows below (Tables 3 and 4):

TABLE 3
Hematologic Alterations in Male and Female Rats
from 90 Day Dietary Administration of Dazomet

	Dose Groups									
	males (ppm)					females (ppm)				
	0	20	60	180	360	0	20	60	180	360
Hb-DAY 47 (mmol/L)	8.9± 0.06	9.1± 0.1	8.9± 0.09	8.9± 0.08	8.8± 0.05	8.8± 0.01	8.8± 0.1	8.8± 0.1	8.8± 0.09	8.6± 0.08
Hb-DAY 86	9.5± 0.1[a]	9.4± 0.07[a]	9.2± 0.08[a]	9.3± 0.1[a]	9.1± 0.08[a,b]	9.4± 0.1[a]	9.2± 0.1[a]	9.2± 0.08[a]	9.1± 0.1	8.8± 0.1[b]

data taken from Tables B035-B036, pages 187-188 of report

[a]significantly different vs value at sample day 47 for the same dose group.

[b]significantly different vs control value from the same sampling time.

As shown in the above summary, a significant decrease in plasma hemoglobin was observed in both sexes at the 360ppm dose level. Other hematological changes observed in this study were incidental and not dose-related.

TABLE 4
Clinical Chemistry Parameters in Male and Female Rats from 90 Day Dietary Administration of Dazomet

	Dose Groups									
	males (ppm)					females (ppm)				
	0	20	60	180	360	0	20	60	180	360
protein-Day 47 (g/L)	63.9± 0.7	63.9± 1.1	62.8± 1.2	60.1± 1.2[b]	59.9± 1.2[b]	64.4± 0.9	61.6± 0.6[b]	59.3± 0.6[b]	60.5± 0.9[b]	58.7± 1.0[b]
protein-Day 86	68.6± 1.1	68.4± 1.0	66.5± 1.0	64.6± 1.1[a,b]	64.1± 0.9[a,b]	69.0± 0.6	66.2± 1.3[a]	64.7± 1.0[a,b]	65.3± 0.9[a,b]	62.6± 1.0[a,b]
albumin-Day 47 (g/L)	38.0± 0.5	36.8± 0.8	36.4± 0.6	36.3± 0.7	36.6± 0.5	39.9± 0.5	37.0± 0.6[b]	36.9± 0.4[b]	36.9± 0.5[b]	36.5± 0.5[b]
albumin-Day 86	39.0± 0.7	39.4± 0.6[a]	38.4± 0.6[a]	37.4± 0.4	38.9± 0.4[a]	41.6± 0.4[a]	38.7± 0.6[b]	39.3± 0.7[a,b]	39.6± 0.5[a,b]	38.2± 0.5[b]
potassium (mmol/l) Day 47	6.2± 0.1	6.2± 0.0	6.2± 0.1	6.1± 0.0	6.2± 0.2	5.9± 0.2	5.4± 0.1	5.5± 0.1	5.6± 0.1	5.3± 0.1
potassium Day 86	5.8± 0.1	6.1± 0.1	5.9± 0.0[a]	5.9± 0.0	5.6± 0.0[a]	6.1± 0.1	5.6± 0.1	5.7± 0.1	5.7± 0.1	5.3± 0.1[b]

data taken from Tables B009-B012 and B025-B026, pages 161-164 and 177-178 of registrant report.

[a]significantly different vs value at sample day 47 for the same dose group.

[b]significantly different vs control value from the same sampling time.

The most significant findings in clinical blood chemistry measurements made over the course of treatment with dazomet in rats was a statistically significant decrease in total protein and albumin in female rats at all dose levels tested on both days 47 and 86, significant decreases in protein in male rats at the 180 and 360ppm dose level, and significant decreases in serum potassium in male and female rats at the 360ppm dose level on day 86. The effects on protein and albumin appear to be more marked on day 47 (in relation to day 86, as no control values (day 0) were reported). Historical control data presented by the registrant (pages 47-48 of the report) show that values for male rats fall within the historical control range, but that values for female rats are in large part outside this range (Figure 4.3.2, page 48 of the report).

8) **Urinalysis:** (Tables B051-B054, pages 205-206)

Urine was collected overnight from each rat 38 and 80 days after study initiation. The following parameters were measured:

- _-_ appearance
- _x_ volume
- _-_ specific gravity
- _x_ protein
- _x_ ketone
- _x_ blood
- _x_ sediment
- _x_ glucose
- _x_ pH
- _x_ bilirubin
- _x_ urobilinogen
- _x_ nitrate
- _-_ color
- _-_ total reducing substances

No significant effects of test article treatment were reported upon analysis of urine from male and female rats at all dose levels.

9) **Anatomic and Histologic Pathology:**

The brain, liver, kidneys, testes, and adrenals were weighed in all animals.The following tissues were examined in situ and then harvested:

Digestive	Respiratory	Urogenital
_-_ tongue	_x_ trachea	_x_ kidneys*
_x_ salivary glands*	_x_ lungs*	_x_ urinary bladder*
_x_ esophagus*	_-_ nasal cavity	_x_ testes*
_x_ stomach*		_-_ epididymides*
_x_ duodenum*		_-_ seminal vesicle*
_x_ jejunum*	_x_ aorta*	_x_ prostate
_x_ ileum*	_x_ heart*	_x_ ovaries
_x_ cecum*	_x_ bone marrow*	_x_ uterus*
_x_ colon*	_x_ lymph nodes*	_x_ vagina
_x_ rectum*	_x_ spleen*	
_x_ liver*	_x_ thymus*	
_x_ pancreas*		

Neurologic	Glandular	Other
_x_ brain*	_x_ adrenals*	_x_ bone
_x_ peripheral nerve*	_-_ lacrimal gland	_x_ skeletal muscle
_x_ spinal cord (3 levels)*	_x_ mammary gland	_x_ skin*
_x_ pituitary*	_x_ parathyroids*	_x_ all gross lesions*
_x_ eyes	_x_ thyroids*	

*EPA guideline requirement "-" not examined

a) Anatomic Pathology:

i) Organ Weights (Tables 037-038, page 92-93 of report)

A statistically significant increase in absolute liver weight was reported for male rats in the 60ppm, 180ppm, and 360ppm dose groups. Liver weight increased from a mean value in control of 11.4g to values of 12.9g, 13.0g, and 12.4g for the 60ppm, 180ppm, and 360ppm dose groups of male rats.
In female rats, a statistically significant decrease in absolute adrenal weight was observed in the 360ppm dose group (from 0.1113g in control rats to 0.0951g in the 360ppm dose group. No other statistically significant changes were reported in male and female rats in absolute organ weights.

ii Organ/Body Weight Ratios (Tables 039-040, pages 94-95 of report).

A significant increase in the liver:body weight ratio was observed in male rats at the 60ppm, 180ppm, and 360ppm dose level, as was an increase in the testes:body weight ratio in the 360ppm dose group.
In female rats, statistically significant increases in the liver:body weight ratio were observed at the 180ppm and 360ppm dose level. Relative weight of the kidneys and brain were significantly reduced in female rats at the 360ppm dose level.

iii) Macroscopic Lesions (Table 041, page 96 of report)

Few macroscopic lesions were reported in this study, and none appeared to be associated with test article treatment.

iv) Microscopic Lesions (Table 042-043, pages 97-98 of report)

According to the registrant (page 50), male rats in the 60ppm, 180ppm, and 360ppm dose groups showed pronounced foci of fatty degeneration in the liver. Female rats in the 180ppm and 360ppm dose groups showed similar changes in the liver as male rats.
No other microscopic lesions were reported which were felt to be related to administration of dazomet in male or female rats.

III. DISCUSSION

In the present study, the subchronic oral toxicity of Dazomet was evaluated in male and female Wistar rats. Test compound was administered in the diet for 90 days. Observations for mortality were made daily, and observations for clinical toxicity were monitored twice daily. Body weight and food consumption were recorded weekly. Clinical pathology (hematology and clinical chemistry), and urinalysis measurements were made during approximately the midpoint of the study and again at study termination. Anatomic and histopathologic examination were performed at study termination on all animals in the control and high dose groups. Selected organs were weighed from

all dose groups of rats including controls.

No mortality or clinical toxicity was observed in male or female rats over the course of this study.

Group mean body weight in male rats from the 360ppm dose group was decreased 7% below control by day 49 of the study, and persisted until study termination, while a similar decrease (10%) was observed in female rats at the same dose level. Body weight was not affected in male or female rats at any other dose level. Overall body weight gain in the 360ppm dose groups of male and female rats was decreased by 13% and 26%, respectively vs controls for the study duration. The lack of test article effect on food consumption and food efficiency in this study supports the idea of a direct effect of test article on body weight.

Alterations in clinical pathology observed in this study were minimal and were confined to the 360ppm dose level. At this dose, significant decreases in hemoglobin were reported for male and female rats at study termination. Although increasing values for this parameter were observed in control rats (Table 3, above), a similar effect occurred in treated rats. Thus, the effect at the 360ppm dose appears treatment related.

Clinical chemistry alterations were observed in treated male and female rats, and involved primarily changes in serum total protein and albumin. Effects in female rats were apparently more marked than in males, as most of the alterations observed in male rats in total protein and albumin fell within historical control data provided by the registrant. However, effects in female rats of test article treatment on serum total protein and albumin appear dose related and are related to treatment with test article.

The effects of test article on serum total protein and albumin in male and female rats may be associated with the increased absolute liver weight and liver:body weight ratio in male and female rats. In male rats, absolute liver weight was increased significantly at the 60ppm, 180ppm, and 360ppm dose level as was the relative liver:body weight ratio. In female rats, liver:body weight ratio was significantly increased at the 180ppm and 360ppm dose level. The increase in liver weight and liver:body weight ratio for both sexes is supported in part by the finding of pronounced foci of fatty degeneration in the livers of both male and female rats at the 60ppm, 180ppm, and 360ppm dose levels. Although this pathological change could increase liver weight, there is no evidence that this pathology would adversely affect the lifespan of the rat, as other treatments (such as phenobarbital) are also known to result in this type of pathology.

Other effects included a significant decrease in relative kidney: and brain:body weight ratios in female rats at the 360ppm dose level, and a significant decrease in absolute adrenal weight in female rats at the 360ppm dose level. The alterations in kidney:body weight, brain:body weight, and absolute adrenal weight in female rats were not supported by concomitant histopathology in these organs at this dose. Thus, the cause of the altered ratios remains unclear from this study. Longer term studies may shed light on this effect.

IV.CONCLUSIONS

Dazomet was administered to male and female Wistar rats at nominal dose levels of 0ppm, 20ppm (30 ppm achieved intake in males [1.5 mg/kg/day]; 34 ppm achieved intake in females [1.7 mg/kg/day]) 60ppm (90 ppm achieved intake in males [4.5 mg/kg/day]; 106 ppm achieved intake in females [5.3 mg/kg/day]), 180ppm (274 ppm achieved intake in males [13.7 mg/kg/day]; 308 ppm achieved intake in females [15.4 mg/kg/day]) and 360ppm (560 ppm achieved intake in males [28.0 mg/kg/day]; 640 ppm achieved intake in females [32 mg/kg/day]). Decreased absolute body weight and body weight gain were observed in male and female rats at the 360ppm dose

level. Statistically significant decreases in serum total protein and albumin were observed at the 60ppm, 180ppm, and 360ppm dose level in male and female rats, but was apparently treatment related only in female rats. Increased absolute liver weight and liver:body weight ratio was observed in male rats from the 60, 180, and 360ppm dose levels. Increased liver:body weight ratio was observed in female rats at the 180 and 360ppm dose levels.

Based upon the results of this study, the systemic NOEL is = 20 ppm, and the systemic LEL is = 60 ppm for male rats (increased liver weight, liver:body weight ratio) and LEL=180ppm for female rats (increased liver:body weight ratio).

The Maximum Tolerated Dose (MTD) appears to have been achieved at 360ppm dazomet (decrease in body weight gain in male and female rats).

V. CLASSIFICATION: Core minimum

This study satisfies the guideline requirements (82-1) for a subchronic oral toxicity study in rats.

Reviewed by: Timothy F. McMahon, Ph.D. 10/11/91
Section I, Toxicology Branch II (H7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. 10/15/91
Section I, Toxicology Branch II (H7509C)

Data Evaluation Report

Study type: Subchronic oral toxicity - dogs
Guideline: 82-1

EPA ID Numbers: MRID number: 418655-01
Caswell No: 840
HED Project Nos: 1-1669

Test material: Dazomet

Synonyms: tetrahydro-3,5-dimethyl-2 H-1,3,5-thiadiazine-2-thione

Study number(s): 87-0456-0001

Title of report: Report on the Study of the Toxicity of Dazomet in Beagle Dogs After 3 Month Administration Via the Diet.

Testing Facilities: BASF Aktiengesellschaft
Department of Toxicology
D-6700 Ludwigshafen
W. Germany

Sponsor: BASF Corporation
Agricultural Chemicals Group
Research Triangle Park, N.C. 27709

Author(s): Dr. Hellwig

Study Completed: September 1987

Conclusions: Dazomet was administered to male and female beagle dogs at dose levels of 0ppm, 25ppm (0.87 mg/kg/day, males; 0.92 mg/kg/day, females), 100ppm (3.5 mg/kg/day, males and females), and 400/200ppm (7.25 mg/kg/day, males; 8.09 mg/kg/day, females). A statistically significant increase in the relative liver: body weight ratio was observed in male and female dogs from the 400/200ppm dose level at study termination. Increased hemosiderosis was also observed in the spleen of male and female dogs at the 400/200ppm dose level. Decreased hemoglobin, erythrocytes, and hematocrit was observed in male and female dogs at the 400/200ppm dose level on study day 90. There did not appear to be any other toxic effects associated with administration of dazomet.

Systemic NOEL = 100ppm (males and females).
Systemic LEL = 400/200ppm (increase in relative liver: body weight ratio; increased hemosiderosis in the spleen of males and females).

Classification: Core minimum

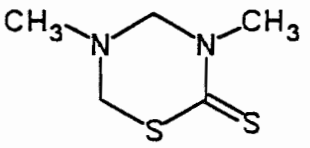
This study satisfies the guideline requirements (82-1) for a subchronic oral toxicity study in dogs.

Data for individual dogs from blood collection point "0", group 1 is missing (pages 336-337 of report).

I. MATERIALS AND METHODS

A. Test Material: Dazomet
average purity: ≥ 98.2% (page 19 of report); batch # 26-5297
description: white powder with a tinge of gray

Structure:



B. Vehicle: dietary preparation

C. Test Animals: Species: purebred beagle dog, male and female
Source: stated to be of BASF's own breed (page 20 of report)
Age: approximately 4-9 months at start of study.
Weight: males, 8.6 (6.6-10.3kg); females, 8.7 (6.7-10.8kg)

D. Animal Husbandry:

Sixteen male and 16 female dogs were used in this study. Dogs were vaccinated with Stagloban P, Candur SHL, Epivax SH + L, and Candur P. Dogs were healthy at the time they were relocated from the breeding unit to individual kennels. Dogs were allowed 8 days acclimation to the laboratory environment before treatment. Dogs were housed singly in kennels measuring 2.0m^2 floor space inside and 7.0m^2 floor space outside. Dogs had continuous access to outside kennels. The animal room was ventilated by a forced air system, while the light/dark cycle corresponded to the natural day/night rhythm. Artificial light was used as required during working hours. A ration of 700g food was offered daily to dogs during adaptation and testing periods. Food consisted of 350g powdered diet (KLIBA laboratory diet "A", Kaiseraugst, Switzerland) which had been made into a paste with 350ml water in a feed bowl immediately before administration. Blended water (fully demineralized water adjusted with drinking water to about 4° German hardness) was available *ad libitum* except during periods of urine collection, when dogs were given 500ml drinking water.

E. Experimental Design and Dosing:

Dogs were randomly assigned upon arrival to study groups using a random number generator based upon equalization of body weight in individual groups.

Four dogs per sex per dose were used. Test groups included control and the following dose groups:

Group #	Dose (ppm)	Animal #s male	female
1	0	1-4	17-20
2	25	5-8	21-24
3	100	9-12	25-28
4	400/200	13-16	29-32

Dose selection for this study was based upon preliminary studies of capsule and dietary administration to beagle dogs. Capsule administration at doses of 320 and 80 mg/kg resulted in frank toxicity (unsteady gait and progressive weakness of the hindlimbs) and severe vomiting, while at a dose of 20 mg/kg few signs were observed. Dietary administration at doses of 12,000, 3,000, and 750ppm resulted in vomiting at all dose levels and considerable loss of body weight. Dogs in this first dietary study were returned to normal feed for 9 days and then used for a second test feeding at doses of 200, 400, and 600ppm test material. At these doses, test material was apparently well tolerated by the dogs. Vomiting occurred only during the first 2 days of administration, and clinical signs consisted of changes in red cell count at 600ppm, and in some dogs at 400ppm. Possible kidney dysfunction in the form of increased urea was observed in one female dog at 600ppm.

Based on these findings, 400ppm was selected as the high dose for the present study. However, it was evident during the first 3 weeks of this study that 400ppm was not well tolerated by dogs. Thus, the dose was reduced to 200ppm on day 24 of the study.

F. Dietary Preparation and Analysis:

Dazomet was incorporated into ground diet at the required concentrations by preparation of a premix in which test substance was "intensely" mixed with a small portion of feed in a beaker using a spatula. Premix was prepared from this by using a Bosch mixer. The premix was then adjusted to the desired concentration with the appropriate amount of feed using a GEBR.LODIGE laboratory mixer. Test diets were prepared twice each week , stored at 4 °C after mixing, and removed from storage only shortly before preparation of the paste for consumption. It was not stated whether the concentration of dazomet was adjusted for body weight gain during the study.

Stability of dazomet was determined prior to study initiation (98.2%) and again at study termination (97%), and was found to be stable over the study period (page 53 of report). Test diets were analyzed for stability and homogeneity of dazomet in food prior to study initiation, approximately 6 weeks after study initiation, and again at study termination. Results (page 54 of report) demonstrated that stability and homogeneity at all dose levels did not vary significantly from target values over the course of the study.

G. Statistical Analysis:

According to the registrant (page 40 of report), statistical analysis of the data was carried out in the Computer Center of BASF Aktiengesellschaft and on the computer systems of the Department of Toxicology.

H. Compliance:

A signed "GLP Statement of Compliance" was provided. This study was conducted in accordance with the OECD principles of Good Laboratory Practice.

A signed statement of "Data Confidentiality Claims" was provided.

A signed "Statement of the Quality Assurance Unit" was provided.

A signed statement of EPA Flagging Criteria was provided.

II. OBSERVATIONS AND RESULTS:

1) **Mortality** : All dogs were checked twice daily for moribund appearance or mortality. Observations were made once a day on weekends and holidays.

No mortality was reported during the study period.

2) **Clinical Observations** : All dogs were checked for evident signs of toxicity at least once a day on workdays. If signs were observed, dogs were observed several times daily.

Vomiting was observed once in 1 male dog from the 25ppm dose group during the first week of test article administration. In the 100ppm dose group, diarrhea was observed three times in 1 male dog during week 2 of test article administration, while gelatinous, partly reddish mucus was observed twice in the feces of one female dog during weeks 7 and 9 of test article administration. The sole clinical sign reported in dogs at the 400/200ppm dose level was vomiting (2 male dogs during weeks 1-4 of the study; 4 female dogs during weeks 1-3 of the study). However, when the dose was reduced to 200ppm, vomiting was no longer observed.

3) **Body Weight:** Body weight data were collected for all dogs 7 days prior to study initiation and then weekly thereafter. Group mean body weights and body weight gains in male and female dogs are summarized in the following Table:

TABLE 1
Group Mean Body Weights (in Kg) in Male and Female Dogs from
90 Day Dietary Administration of Dazomet[a]

	Dose Groups							
	males (ppm)				females (ppm)			
Days on Test	0	25	100	400/200	0	25	100	400/200
0	8.5± 1.3	8.7± 0.8	8.6± 1.4	8.6± 1.1	8.7± 0.9	8.9± 1.3	8.9± 0.6	8.3± 0.2
7	8.6± 1.4	8.9± 0.6	8.5± 1.6	8.2± 1.3	8.8± 0.8	9.1± 1.3	8.9± 0.7	7.5± 1.3
14	8.9± 1.4	9.2± 0.6	8.9± 1.5	8.0± 1.7	9.0± 0.8	9.3± 1.2	9.1± 0.8	6.9±* 1.3
21	9.1± 1.4	9.5± 0.5	9.2± 1.5	8.1± 1.8	9.2± 0.8	9.5± 1.1	9.4± 0.8	6.7±* 1.4
49	9.9± 1.2	10.3± 1.4	10.1± 1.3	9.5± 1.7	9.8± 0.7	9.9± 1.2	9.9± 0.9	7.5± 1.9
91	10.7± 1.2	11.4± 0.4	10.8± 0.9	10.4± 1.4	10.4± 0.7	10.2± 1.0	10.4± 0.9	8.2± 1.8

Data from Tables A 027-A030, pages 159-162 of registrant report, N=4.
*$p < 0.05$ vs control by Kruskal-Wallis ANOVA and Mann-Whitney U-test.

Group mean body weight gain over the course of the study at selected times is summarized below (Table 2):

TABLE 2
Group Mean Body Weight Gain (in Kg) in Male and Female Dogs from 90 Day Dietary Administration of Dazomet[a]

	Dose Groups							
	males (ppm)				females (ppm)			
Days on Test	0	25	100	400/200	0	25	100	400/200
0-21	0.7± 0.1	0.8± 0.3	0.6± 0.4	-0.5± 0.9	0.5± 0.2	0.6± 0.3	0.5± 0.2	-1.7±* 0.5
21-49	0.6± 0.1	0.8± 0.2	0.9± 0.2	1.2± 0.1	0.6± 0.06	0.3± 0.04	0.5± 0.09	0.8± 0.3
49-91	0.8± 0.08	1.0± 0.04	0.7± 0.2	0.9± 0.19	0.5± 0.05	0.3± 0.1	0.4± 0.1	0.6± 0.2
0-91	2.2± 0.3	2.7± 0.8	2.2± 0.9	1.9± 0.5	1.7± 0.2	1.3± 0.4	1.5± 0.3	-0.2± 1.0

Data from Tables A 031-A 034, pages 163-166 of registrant report, N=4

No significant effects of test article administration on body weight and body weight gain were observed in male or female dogs from the 25 and 100ppm dose levels. In male dogs receiving 400/200ppm test material, group mean body weight was decreased 11% vs control between 0-21 days of treatment (Table 1, above). However, this decrease was not statistically significant. Body weight in this dose group rebounded to a mean weight similar to controls when the dose was decreased to 200ppm. In female dogs at the 400/200ppm dose level, a similar phenomenon was observed (Table 1, above) from days 0-21, but group mean body weight was decreased 27% vs control ($p < 0.05$). In addition, final body weight of this dose group was decreased 21% vs control. This result was apparently due to loss of body weight in two female dogs (kennel # 30 and 31) which persisted in comparison to the other two dogs in this dose group (Table A029-A030, pages 161-162 of report). In male dogs, final body weight was similar among dose groups at study termination (10.4-11.4kg). Cumulative body weight change in female dogs at the 400/200ppm dose level was significantly decreased vs. other dose groups for the entire study (Table 033, page 98 of report).

4) **Food Consumption:** Food was offered to dogs daily generally in the late morning for one hour. It should be noted (page 53 of report) that the nominal % of test article had declined to 65% after one hour in the pasted feed. Food consumption was recorded each day for male and female dogs (Tables 001-026, pages 66-91 of report). Feed not consumed in the one hour period was weighed and subtracted from the amount offered. Data on food efficiency were provided for each test group at weekly intervals. The following formula was used to calculate food efficiency:

$$\frac{BW_{x+n} - BX_x}{F_y}$$

BW_{x+n} = mean body weight on day x+ 7

BW_x = mean body weight on day x

F_y = mean food consumption from days 0-6, 7-13, etc. divided by 2. Food consumption was divided by 2 because half of the feed ration consisted of water.

Food consumption was apparently equivalent in male and female dogs in the 0, 25, and 100ppm dose groups over the duration of the study. At the 400/200ppm dose level, however, food consumption was decreased over the period during which dogs received 400ppm test article (Tables 001-026, pages 66-91 of report). This decrease in food consumption was more evident in female dogs, and was apparently due to the decreased food consumption in the two female dogs which showed the greatest decrease in body weight gain (kennels 30 and 31). Total food consumption in control male dogs from days 0-21 was calculated as 15,028.3g , while consumption in control female dogs for the same time period was 14,226.8g . Food consumption in male and female dogs from the 400/200ppm dose group for days 0-21 of the study, was, however, not equivalent (9,754.6g vs 5,359.9g in males and females, respectively). Food consumption in the 400/200ppm dose groups appeared to recover to levels similar to control dogs after the 400ppm dose level was decreased to 200ppm. Thus, palatability of test diet appears to have been a factor in the decreased food consumption at the 400/200ppm dose level.

Food efficiency, similar to that seen with body weight and food consumption, was affected primarily in the first 3 weeks of the study among dogs in the 400/200ppm dose group (Tables 035-036, pages 100-101 of report). Food efficiency did not appear to differ significantly in treated vs control dogs following the decrease from 400ppm to 200ppm in the diet of high dose dogs.

The reported patterns of food consumption, body weight gain, and food efficiency in male and female dogs appear to be related to test article administration insofar as a dietary level of 400ppm resulted in poor palatability of the diet, leading to decreased body weight gain and food efficiency. Thus, toxicity of test article was evident at 400ppm, but decreasing the dietary level to 200ppm resulted in a reversal of the effects on body weight and food consumption. Thus, 200ppm dazomet did not appear to have significant effects on body weight gain and food consumption in this study.

5) **Intake of Dazomet:** Intake of test chemical was calculated at the same time intervals as for body weight (day 0 of the study, and weekly thereafter). Data for test article intake over the course of the study are summarized below (Table 3):

TABLE 3
Intake of Dazomet in Male and Female Beagle Dogs

Dose levels(ppm)	Nominal Intake (mg/kg/day)	Mean Actual Intake (mg/kg/day) males	females
0	0	—	—
25	0.625	0.87 (139)[b]	0.92 (147)
100	2.5	3.5 (140)	3.5 (140)
400/200	10/5[a]	7.25 (145)	8.09 (160)

[a]values calculated from day 28-91, when nominal intake was 200ppm.
[b]percent of nominal intake

Note: The registrant apparently used a value of 200ppm test article for calculations of test article intake on days 0, 7, 14, and 21, when dogs actually received 400ppm test article.

According to the intake data supplied, intake of test article appeared to be in excess of nominal intake at all dose levels for the study duration.

6) **Ophthalmologic Examination:** Ophthalmoscopic examination was performed on all dogs prior to study initiation and at the end of the study. Examinations were made with a KOWA camera. Results, as summarized in Table 042, page 107 of the report, showed no ophthalmologic abnormalities in male or female dogs at either time of examination.

7) **Clinical Pathology:**

Blood samples were obtained from the vena cephalica antebrachii of all dogs 1 day before test article administration, and again at 47 and 90 days after study initiation. Blood samples were analyzed in random sequence. At study termination, dogs were weighed, anesthetized and sacrificed by exsanguination from the cervical and brachial vessels. Absolute and relative weights of the liver, kidney, thyroid, and testes were determined. Tissue samples were preserved in 4% formaldehyde solution, followed by histochemical processing (H&E stain) and examination by light microscopy. Liver from control and high dose dogs was stained additionally with ORO stain.

a) Hematology: The following CHECKED parameters were measured:

- x total leucocyte count*
- x erythrocyte count*
- x hemoglobin*
- x hematocrit*
- x platelet count
- x total plasma protein
- x leukocyte differential*
- x mean corpuscular HGB
- x mean corpusc. HGB conc.
- x mean corpusc. volume

_-_ packed cell volume	_x_ thromboplastin time*
_x_ activated partial thromboplastin time	_x_ Heinz bodies
_x_ methemoglobin	

*EPA guideline requirement "-" not examined

The above hematological parameters (with the exception of clotting analysis) were performed using a Coulter Counter, S-plus model. Clotting analysis was carried out using a ball coagulometer (Amelung, KC10 model). Reticulocytes (methylene blue stain) and Heinz bodies (methyl violet stain) were counted visually; methemoglobin was determined photometrically.

The best assessment of hematological data can be made from examination of Tables B039-B054, pages 219-234 of the report and comparison to Tables 049-050, pages 112-114 of the report. Relevant hematological changes are summarized below (Table 4):

TABLE 4
Hematologic Alterations in Male and Female Dogs
from 90 Day Dietary Administration of Dazomet

	Dose Groups							
	males (ppm)				females (ppm)			
	0	25	100	400/200	0	25	100	400/200
Hb- DAY 0 (mmol/L)	8.2±0.08	8.1±0.12	8.0±0.17	8.4±0.36	9.2±0.34	8.9±0.18	9.3±0.23	8.5±0.23
Hb- DAY 47	9.1±0.07 [a]	9.0±0.45	8.8±0.21	8.5±0.28	9.9±0.33	9.5±0.29	9.9±0.26	7.8±0.20 [b]
Hb-DAY 90	9.5±0.07 [a]	9.6±0.25 [a]	9.4±0.33	8.9±0.20 [b]	10.0±0.20	10.0±0.28 [a]	10.2±0.35	8.3±0.16 [b]
Ery- DAY 0 (tera/L)	5.8±0.06	5.7±0.14	5.6±0.14	5.8±0.14	6.2±0.16	6.3±0.07	6.5±0.23	6.0±0.21
Ery-DAY 47	6.4±0.06 [a]	6.4±0.27	6.2±0.20 [a]	6.0±0.17	6.8±0.18	6.7±0.16 [a]	6.9±0.16	5.5±0.16 [b]
Ery-DAY 90	6.6±0.04 [a]	6.7±0.08 [a]	6.6±0.27 [a]	6.1±0.14 [b]	6.7±0.07 [a]	6.9±0.13 [a]	7.0±0.2	5.8±0.10 [b]

Table 4, cont.

	Dose Groups							
	males (ppm)				females (ppm)			
	0	25	100	400/200	0	25	100	400/200
Ht - DAY 0 (L/L)	0.39±0.00	0.39±0.00	0.38±0.00	0.4±0.01	0.44±0.01	0.42±0.01	0.45±0.01	0.41±0.01
Ht - DAY 47	0.43±0.00 [a]	0.43±0.02	0.42±0.01 [a]	0.4±0.01	0.47±0.01	0.46±0.01	0.47±0.01	0.38±0.00 [a,b]
Ht - DAY 90	0.45±0.00 [a]	0.45±0.01 [a]	0.45±0.01 [a]	0.42±0.01	0.47±0.01	0.47±0.01	0.49±0.01	0.4±0.00 [b]

data taken from Tables B039-B044, pages 219-224 of report

[a]significantly different vs value at sample day 0 for the same dose group.

[b]significantly different vs control value from the same sampling time.

As shown above and as suggested by the data in this study, the most significant changes in hematology were observed with hemoglobin (Hb), hematocrit (Ht), and erythrocytes (Ery). Statistically significant decreases in hemoglobin, erythrocytes, and hematocrit were observed in male and female dogs at the 400/200ppm dose level on day 90 of the study. In female dogs at the 400/200ppm dose level, significant decreases in these parameters were also observed on day 47. While this effect appears test article related, it must be noted that values for these parameters in control dogs showed increasing values over the time course of this study. In some cases, as in male dogs at days 47 and day 90, these increases become statistically significant.

b) Blood Chemistry: The following CHECKED parameters were measured:

__x__ glucose*
__x__ albumin*
__x__ globulin (calculated)
__x__ creatinine*
__x__ total bilirubin*
__-__ direct bilirubin
__-__ indirect bilirubin
__x__ urea nitrogen*
__x__ total protein*
__-__ uric acid
__x__ calcium*
__x__ phosphate*
__x__ sodium*
__x__ potassium*
__x__ phosphorous

__x__ AST(SGPT)*
__x__ ALT(SGOT)*
__x__ alkaline phosphatase
__-__ creatine phosphokinase
__-__ lactate dehydrogenase
__-__ sorbitol dehydrogenase
__-__ gamma glutamyl trans-peptidase

__x__ triglycerides
__x__ cholesterol
__x__ chloride*

*EPA guideline requirement "-" not examined

Clinical chemistry parameters were determined using an automatic analyzer (GSA II, Greiner Electronics). SGOT, SGPT, and ALK-PHOS activities were determined using an automatic enzyme analyzer (ACP 5040, Eppendorf).

Clinical chemistry parameters in male dogs appeared relatively unaffected by treatment with test article (Table 043, page 108 of report). In female dogs, several significant changes were noted in clinical chemistry parameters (Table 044, page 109 of report), but in light of the variations seen in values for control dogs over time in these parameters, it does not appear that these alterations were unequivocally the result of treatment with test article. Reduction in total protein in female dogs from the 400/200ppm dose group (Table B012, page 192 of report) is an apparent dose-related effect, but may be based upon the decreased food consumption and body weight of dogs in this dose group.

8) **Urinalysis:**

Overnight urine collection was conducted on all dogs 6 days prior to test article administration, and again at 44 and 86 days after study initiation. Urine parameters (with the exception of sediment and specific gravity) were measured semiquantitatively using Clini-Tek urine test strips and a reflecting photometer. Specific gravity was determined with a urine refractometer and sediment was evaluated microscopically. The following parameters were measured:

x appearance	x glucose
x volume	x pH
x specific gravity	x bilirubin
x protein	x urobilinogen
x ketone	- triple phosphate crystals
x blood	- color
- casts	- bacteria
x- mucous	- epithelial cells

No significant effects of test article treatment were reported upon analysis of urine from male and female dogs at all dose levels.

9) **Anatomic and Histologic Pathology:**

The thyroid, liver, kidneys, adrenals and testes were weighed in all dogs. All gross lesions were examined in affected dogs. The following tissues were examined macroscopically, and then preserved for histopathological examination:

Digestive	Respiratory	Urogenital
- tongue	x trachea	x kidneys*
x salivary glands*	x lungs*	x urinary bladder*
x esophagus*	- nasal cavity	x testes*

(cont.)

x stomach*	- tonsils	x epididymides*
x duodenum*		- seminal vesicle*
x jejunum*	x aorta*	x prostate
x ileum*	x heart*	x ovaries
x cecum*	x bone marrow*	x uterus*
x colon*	x lymph nodes*	x vagina
x rectum*	x spleen*	
x liver*	x thymus*	
x pancreas*		
x gallblader		

Neurologic	Glandular	Other
x brain*	x adrenals*	x bone (femur)
x peripheral nerve*	- lacrimal gland	x skeletal muscle
x spinal cord (3 levels)*	x mammary gland	x skin*
x pituitary*	x parathyroids*	x all gross lesions*
x eyes	x thyroids*	

*EPA guideline requirement "-" not examined

a) Anatomic Pathology:

i) Organ Weights

In male dogs, a 12% increase in absolute liver weight was reported in dogs from the 100 and 400/200ppm dose groups (317.5g vs 357g, respectively). A 32% decrease in absolute weight of the testes (from 17.2g to 13.0g) was also reported, as was a 45% increase in thyroid weight (0.6628g vs 0.9668g). In female dogs, decreased absolute weight of kidneys and thyroid was also observed (from 49.1 to 41.5g for kidneys, a decrease of 20%; and from 0.7415 to 0.6395g for thyroid, a 165 decrease). Relative organ weight of the liver was affected in both male and female dogs. In males, an increase in relative liver weight from 2.96 to 3.3 and 3.4 ($p < 0.05$ and 0.01, respectively) was observed at 100ppm and 400/200ppm, while in female dogs, a significant increase in relative liver weight was observed at the 400/200ppm dose level (from 3.0 to 3.6g, $p < 0.01$). No corresponding abnormality in histology was observed in livers from animals in these dose groups. For female dogs, this relative increase may be due to the decreased (21%) terminal body weight of the 400/200ppm dose group. However, terminal body weights of male dogs were equivalent. Thus, the increase in relative liver weight in male dogs appears test article related.

ii) Macroscopic Lesions

No abnormalities in gross pathology related to test article administration were observed in this study (page 121 of report).

iii) Microscopic Lesions

According to the registrant (page 60 of report), marked hemosiderosis was observed in the spleen of all male and female dogs of the 400/200ppm dose group. Hemosiderosis was also observed in dogs from the other dose groups, but not to the extent observed in the 400/200ppm dose group. All other histopathological changes observed in this study were considered spontaneous and were not attributed to treatment with test article.

III. DISCUSSION

In the present study, the subchronic oral toxicity of dazomet was evaluated in male and female beagle dogs by administration of test compound in the diet for 90 days. Observations for mortality were made once a day, and observations for clinical toxicity were made twice daily except on weekends. Body weight was recorded weekly, and food consumption was measured daily. Clinical pathology (hematology and clinical chemistry) measurements were made prior to study initiation, and again on study days 47 and 90. Urinalysis was conducted 6 days prior to study initiation and again at 44 and 86 days. Ophthalmoscopic examination was performed prior to the start of the study and again at study termination. Anatomic and histopathologic examination were performed at study termination on all animals. Selected organs (liver, kidney, thyroid, testes) were weighed from all dose groups of dogs including controls.

No mortality was reported in this study. Clinical toxicity was apparent at the start of the study when dogs were given 400ppm test material, and included vomiting and diarrhea. Clinical toxicity was no longer evident when the dose was reduced to 200ppm.

Body weight and body weight gain were affected primarily in the 400/200ppm dose group, when dogs were receiving 400ppm test material. In male dogs, an 11% decrease in group mean body weight was observed during the period of 400ppm test article administration, which rebounded after the dose was reduced to 200ppm. A similar phenomenon was observed in female dogs during the 400ppm dosing period, but the effects appeared more severe (27% decrease in group mean body weight, and decreased mean body weight at study termination). However, these effects were due to relatively severe effects in 2 female dogs. Thus, no significant effects on body weight were observed when the dose was reduced to 200ppm test material. Food consumption and food efficiency were affected in a manner similar to body weight, i.e. observable effects a the 400ppm dose level, but a reversal of effects when the dose was decreased to 200ppm.

Alterations in hematology were observed for hemoglobin, hematocrit, and erythrocytes at the 400/200ppm dose level in both male and female dogs (Table 4, above). Significant decreases in these parameters were observed for both sexes at 90 days, and were also observed in female dogs on day 47 of the study. These effects are considered treatment related despite the variation in control values which occurred in thi study.

No abnormal gross pathology was observed in any tissue examined in this study. With regards to microscopic pathology, however, increased hemosiderosis was reported in the spleen of dogs from the 400/200ppm dose group. No other microscopic pathology was reported as related to test article administration.

Organ weights were affected in male and female dogs receiving 400/200ppm test material. In males, significant increases in liver and thyroid weight were observed, while testes weight was significantly decreased. No corresponding weight was reported for ovaries in female dogs, while thyroid weight was decreased at the 400/200ppm dose in female dogs, in contrast to males. An

effect occurring in both sexes was the significant increase in terminal liver:body weight ratio. No microscopic pathologic abnormality was reported in liver as related to test article administration. In females, this relative increase could be ascribed to relatively severe weight loss in 2 female dogs over the course of the study. However, no significant differences were observed in terminal body weight were observed in male dogs. Thus, the increased liver: body weight ratio in males appears test article related.

IV.CONCLUSIONS

Dazomet was administered to male and female beagle dogs at dose levels of 0ppm, 25ppm (0.87 mg/kg/day, males; 0.92 mg/kg/day, females), 100ppm (3.5 mg/kg/day, males and females), and 400/200ppm (7.25 mg/kg/day, males; 8.09 mg/kg/day, females). A statistically significant increase in the relative liver: body weight ratio was observed in male and female dogs from the 400/200ppm dose level at study termination. Increased hemosiderosis was also observed in the spleen of male and female dogs at the 400/200ppm dose level. Decreased hemoglobin, erythrocytes, and hematocrit was observed in male and female dogs at the 400/200ppm dose level on study day 90. There did not appear to be any other toxic effects associated with administration of dazomet.

Systemic NOEL = 100ppm (males and females).
Systemic LEL = 400/200ppm (increase in relative liver: body weight ratio; increased hemosiderosis in the spleen of males and females).

V. CLASSIFICATION Core minimum

This study satisfies the guideline requirements (82-1) for a subchronic oral toxicity study in dogs.

Data for individual dogs from blood collection point "0", group 1 is missing (pages 336-337 of report).

Reviewed by: Timothy F. McMahon, Ph.D. 10/15/91
Section I, Toxicology Branch II (H7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. 10/15/91
Section I, Toxicology Branch II (H7509C)

Data Evaluation Report

Study type: Chronic Toxicity - rats
Guideline: 83-1a

EPA ID Numbers: MRID number: 418654-01
Caswell No: 840
HED Project No: 1-1900

Test material: Dazomet

Synonyms: tetrahydro-3,5-dimethyl-2 H-1,3,5-thiadiazine-2-thione

Study number(s): 70C0318/8583

Sponsor: BASF Corporation
Agricultural Chemicals Group
Research Triangle Park, NC

Testing Facility: BASF Aktiengesellschaft
Department of Toxicology
W. Germany

Title of report: Report on the Oral Toxicity of Dazomet In Rats After 24 Months Administration in the Diet

Author(s): Dr. B. Kunbroth

Study Completed: July, 1989

Conclusions:

Technical Dazomet was administered to male and female rats in the diet for 104 weeks at doses of 0, 5ppm (0.23 mg/kg/day males; 0.29 mg/kg/day females), 20ppm (0.94 mg/kg/day males; 1.19 mg/kg/day females), 80 ppm (3.81 mg/kg/day males; 5.09 mg/kg/day females), and 320 ppm (16.36 mg/kg/day males; 21.54 mg/kg/day females) in order to determine the toxic effects from chronic administration of this chemical. Reduced group mean body weight and body weight gain was observed in male and female rats at the 320ppm dose level. Significant decreases in hematologic

parameters (red blood cells, hemoglobin, hematocrit) were observed in female rats at the 80 and 320ppm dose level, as were significant decreases in serum albumin, total protein, and globulins, and a significant increase in platelets at 80 and 320ppm dazomet. Male rats showed slight increases in platelets at the 320ppm dose level and a significant increase in serum cholesterol at the 80 and 320ppm dose levels. Relative liver : body weight was also increased in male rats at the 320ppm dose level, but no significant organ weight increases were observed in female rats.

The No Observed Effect Level (NOEL) = 20 ppm

The Lowest Observed Effect Level (LEL) = 80 ppm (decrease in serum albumin, globulins, total protein, hemoglobin, hematocrit, and red blood cells in female rats; increased serum cholesterol in male rats).

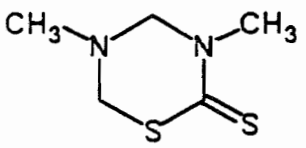
V. CLASSIFICATION
Core Guideline

This study satisfies the guideline requirements (83-1) for a chronic toxicity study in rats.

I. MATERIALS AND METHODS

A. Test Material

Dazomet
purity:98.2%; batch # 26-5297
description: not given in this study; described as a "white powder with a tinge of gray " in MRID# 418655-01.
structure:



B. Vehicle:

dietary preparation

C. Test Animals:

Species: Wistar rat (Chbb=THOM [SPF]), male and female
Source: Dr. Karl Thomae, Biberach an der Riss, FRG.
Age: 42 days old at study initiation.
Weight (mean): males, 182g (range:166-196g); females, 145g (range: 125-158g).

D. Dietary Preparation and Analysis

Dazomet was incorporated into ground diet at the required concentrations by weighing the required amount of test substance and mixing with a small amount of food in a beaker using a spatula. This premix was subsequently prepared in a BOSCH household mixer. Additional amounts of food were then added to the premix to obtain the desired final concentration, and mixing was carried out in a GEBR.LODIGE laboratory mixer for 10 minutes. Test diets were prepared twice a week and stored at 4 °C as soon as possible after mixing.

Stability and purity of test substance at room temperature for the duration of the study was stated to have been performed prior to the start of the present study (page 27 of the report). Stability of test material in ground feed at room temperature was shown to be 1 day as reported on page 1455 of the report. The registrant stated, however (page 27 of the report) that the stability of test material in ground feed was 2 days at room temperature, and provided data in support of this (page 1452 of the report). Stability of test material in ground feed at 4 °C was 4 days (page 1455 of the report). During the conduct of the study, samples of feed were analyzed for test material concentration approximately every six weeks. Food given to the rats was changed daily during the first 2 study

days, and every other day thereafter, as stability of test material for 2 days in feed could be verified.

Homogeneity of test material in feed was checked using samples from the5, 20, and 320ppm dose levels taken at the beginning of the study. Results (page 1453-1454 of the report) showed that for a nominal dietary concentration of 5ppm, actual concentrations of test material ranged from 79-89% of nominal. For a nominal dietary concentration of 20ppm, actual concentrations ranged from 95-106% of nominal. At a nominal dietary concentration of 320ppm, actual concentrations ranged from 95-99% of nominal.

TABLE 1

Analysis of Test Diet Samples[a]

	Dazomet found (ppm)			
Study Week (approx.)	5ppm[b]	20ppm	80ppm	320ppm
0	--	16.7	69.1	299
6	--	17.3	76.5	289
11	4.1	17.0	68.8	292
16	4.4	17.5	69.2	303
28	4.4	17.0	68.1	290
53	4.2	19.4	68.0	307
78	4.8	16.0	65.3	299
104	4.5	17.8	72.4	294

[a]data from pages 1457-1475 of report

[b]samples from the 5ppm dose group were not sent for analysis during the first five weeks of the study. No reason was stated for this omission.

Dietary concentrations of dazomet ranged from 4.1-4.8 ppm in the 5 ppm dose group, from 16.0-19.4 ppm in the 20 ppm dose group, and from 65.3-76.5 ppm in the 80 ppm dose group. In large part, dietary concentrations of test article at all dose levels were not within 10% of nominal concentrations. For the sampling times listed above, the average dietary concentration at 5ppm was 12% below nominal, 14% below nominal at 20ppm, and 13% below nominal at 80ppm. Thus, the average dose level at these doses would be 4.4ppm , 17.2ppm , and 69.6ppm , respectively.

D. Animal Husbandry

One hundred male and 100 female rats were used in this study. Rats were free from any signs of disease upon receipt. Rats were acclimated to the laboratory environment for 8 days prior to test article administration.

Rats were housed singly during test article administration in type DK III stainless steel wire mesh cages (Becker and Co., FRG). Rats were assigned to the various test groups 1 day prior to study initiation according to random allocation based upon body weight. All rats had free access to food

(Kliba 343 rat/mouse/hamster maintenance diet) and drinking water during acclimation and test article administration. Rats were housed in temperature (20-24 °C) and humidity (30-70%) controlled rooms.

One day prior to study initiation, each rat was randomly assigned by computerized random number generation to the various treatment groups as outlined below:

Group #	Dose Level (ppm)	No. of rats (animal #'s) male	female
0	0	20 (1-20)	20 (101-120)
1	5	20 (21-40)	20 (121-140)
2	20	20 (41-60)	20 (141-160)
3	80	20 (61-80)	20 (161-180)
4	320	20 (81-100)	20 (181-200)

E. Statistical Analysis

From page 41 of the registrant's report: "The statistical evaluation and calculation of the data was carried out on the computer systems of the Department of Toxicology (Dr. H.D. Hoffmann, responsible)." A copy of statistical procedures employed is attached.

F. Compliance

A signed data confidentiality claim statement was provided.

A signed statement of GLP compliance was provided. This study was conducted according to OECD guidelines.

A signed statement of quality assurance was provided.

a signed statement of EPA flagging criteria was provided.

II. OBSERVATIONS AND RESULTS

A. Mortality

All rats were observed for moribundity and mortality twice daily during weekdays, and once daily on weekends during the course of the study.

Cumulative mortality in male and female rats is summarized in the following Table:

TABLE 1
Cumulative Mortality in Rats Given Dazomet in the Diet for 24 Months [a]

Week of Study	Males					Females				
	0	5	20	80	320	0	5	20	80	320
1	0(0)[b]	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
13	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
26	1(5)	0(0)	0(0)	1(5)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
52	2(10)	0(0)	0(0)	1(5)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
78	3(15)	1(5)	0(0)	5(25)	0(0)	0(0)	2(10)	0(0)	0(0)	0(0)
91	4(20)	3(15)	3(15)	6(30)	0(0)	1(5)	3(15)	1(5)	2(10)	1(5)
104	5(25)	8(40)	7(35)	9(45)	4(20)	5(25)	6(30)	3(15)	8(40)	3(15)

[a] data taken from pages 119-120 of registrant report.

[b] cumulative mortality (percent mortality). Data for week 1 of the study not specifically provided, but survival assumed to be 100%, as survival was 100% up to week 13 (page 1097 of the report).

Survival did not appear to be affected in treated groups of rats of either sex in comparison to concurrent controls.

B. Body Weights

Body weights of all rats were determined once a week for the first 3 months of the study, and at monthly intervals thereafter. Body weight change was recorded as the difference between body weight on the day of weighing and body weight on day 0 of the study. Group mean body weights at selected times are presented in Table 2

TABLE 2
Group Mean Body Weights in Male and Female Rats Given Dazomet in the Diet for 104 Weeks [a]

Week of Study	Males (g) 0	5	20	80	320	Females (g) 0	5	20	80	320
0	183.4	181.9	180.6	181.0	181.9	146.5	145.6	144.5	144.6	146.0
2	270.6	268.0	265.1	269.5	261.0	187.8	183.0	180.8	182.7	174.8 [c]
13	461.8	458.8	456.3	466.0	437.5	269.9	268.6	266.9	271.1	255.9
53	642.3	675.3	653.7	661.7	617.3	324.2	331.8	334.3	338.5	303.6
104	759.8	847.3	706.7	741.4	669.7	400.7	410.7	421.3	411.2	368.6

[a]data taken from Tables 011-020 and 022-025, pages 77-86 of the report.
[b]p <0.05 vs control; [c]p <0.01 vs control

Group mean body weight in male rats of the 320ppm dose group was slightly depressed (approx. 4%) in comparison to controls for most of the study. Terminal group mean body weight in male rats from the 320ppm dose group (669.7±80.7g) was, however, decreased by 12% in comparison to controls at the end of the study (759.8± 108.3). In female rats of the 320ppm dose group, group mean body weight was decreased vs control by 7-8% from days 14-63 of the study, and this decrease was noted as statistically significant by the registrant (pages 82-83 of the report). However, no statistically significant differences in group mean body weight were observed at any time subsequent to this observation. Terminal body weight in female rats of the 320ppm dose group (368.6 ± 49.3) was decreased by 8% in comparison to concurrent controls (400.7±64.9).

Changes in group mean body weight gain are summarized below for the 104 week study period (Table 3):

TABLE 3
Group Mean Body Weight Gain in Male and Female Rats Given Dazomet in the Diet for 104 Weeks [a]

Week of Study	Males (ppm) 0	5	20	80	320	Females (ppm) 0	5	20	80	320
Body weight week 0 (g)	183.4	181.9	180.6	181.0	181.9	146.5	145.6	144.5	144.6	146.0
Weight gain (grams):										
0-13	278.4	276.8	275.8	284.9	255.6	123.4	123.1	122.4	126.5	109.9
%control	-	99	99	102	91	-	100	99	102	89
0-53	459.3	493.4	473.1	481.4	435.3	177.7	186.3	189.8	193.8	157.6
%control	-	107	103	104	94	-	104	106	109	88
0-104	576.6	664.7	526.4	563.5	488.1	254.7	264.6	276.8	266.9	222.5
% control	-	115	91	97	85	-	103	108	104	87

[a] data calculated from Tables 021-030, pages 87-96 of the report.
[b] $p < 0.05$ vs control; [c] $p < 0.01$ vs control.

Group mean body weight gain in male rats was primarily decreased at the 320ppm dose level, where weight gain was decreased approximately 9% in this dose group compared to controls on day 91 of the study. Overall weight gain in male rats from the 320ppm dose group was decreased by 15% in comparison to control rats, but this difference was not identified as statistically significant. Other dose groups did not appear to be affected in any significant manner. In female rats from the 320ppm dose group, body weight gain from days 14-63 of the study was significantly decreased in comparison to control female rats, a reflection of decreased group mean absolute body weights during this period. This decrease in body weight gain averaged between 15-30% for study days 14-63. Subsequent to this, weight gain in female rats from the 320ppm dose group was approximately 12% less than in control rats. Overall weight gain in female rats from the 320ppm dose group was 13% less than in control rats. Other dose groups did not appear to be affected

C. Food Consumption and Efficiency

Food consumption was calculated for each rat once a week for the first 3 months of the study, and at monthly intervals thereafter. Food efficiency was calculated using the following formula:

$$\frac{BW_x - BX_{x-y}}{FA \times y} \times 100$$

BW_{x-y} = mean body weight at weighing prior to day x

BW_x = body weight on day x

FA = food consumption from day x-y to day x

y = interval in days between weighings

Group mean food consumption at selected time points is summarized in the following table (Table 4):

TABLE 4
Group Mean Food Consumption in Male and Female Rats Given Dazomet in the Diet for 104 Weeks [a]

Week of Study	Food consumption (g/rat/day) Males (g) 0	5	20	80	320	Females (g) 0	5	20	80	320
1	26.0	26.3	26.2	26.4	25.2	18.2	18.0	17.9	19.3	18.0
13	24.0	27.0[c]	26.7[c]	26.7[c]	24.5	15.9	18.4[c]	17.8[b]	19.3[c]	18.8[c]
53	26.6	29.1	29.0	28.8	29.0	19.6	22.3[b]	22.9[b]	23.3[c]	20.9
104	27.5	31.6	26.2	34.3[c]	28.8	21.4	23.9	25.7[b]	25.6	22.5

[a]data taken from Tables 001-010, pages 67-76 of the report.

Food consumption in male rats from the 5, 20, and 80ppm dose groups was increased by 12, 11, and 10% at week 13 of the study ($p < 0.01$), while food consumption in female rats from the 5, 20, 80, and 320ppm dose groups was increased by 15, 11, 21, and 18% in comparison to controls ($p < 0.01$). At week 53 of the study, food consumption in female rats was observed to be significantly increased in the 5, 20, and 80ppm dose groups by 13, 16, and 18%. No increase in food consumption was observed in male rats at this time point. At week 104 of the study, food consumption in male rats was slightly increased at all doses except the 80ppm dose, where a significant increase of 24% was observed. In female rats, food consumption at 104 weeks was increased significantly (20%) only at the 20ppm dose, with a slight increase observed at other doses.

Group mean food efficiency at selected times is presented in the following table (Table 5)

TABLE 5
Group Mean Food Efficiency in Male and Female Rats Given Dazomet in the Diet for 104 Weeks [a]

Food efficiency (b.w. gain/food consumed)

Week of Study	Males (g) 0	5	20	80	320	Females (g) 0	5	20	80	320
1	23.8	23.7	23.3	24.6	22.0	16.2	15.2	16.0	15.3	12.3[c]
7	10.3	9.4	9.3	10.1	9.5	7.4	5.5	6.3	5.5	6.9
13	4.3	3.0	2.6	2.5	1.2[c]	-0.1	0.1	1.3	-0.1	0.2
1-13[d]	11.6	11.3	11.2	11.5	10.7	7.2	6.8	6.9	6.7	6.1

[a]data taken from Tables 031-032 and 036-037, pages 97-98 and 102-103 of the report.
[b]$p < 0.05$ vs control; [c]$p < 0.01$ vs control.
[d]calculated from group mean food efficiency for weeks 1-13.

Food efficiency in female rats was significantly decreased by 25% at the 320ppm dose level during week 1 of the study. No other changes were observed at this time point. At week 13, the only change observed was in male rats from the 320ppm dose group, where food efficiency was decreased by 72% compared to control. Although significant changes occurred during weeks 1-13 of the study in both sexes, overall food efficiency (weeks 1-13 inclusive) was not significantly affected in male rats, but a 16% decrease in overall food efficiency was observed in female rats from the 320ppm dose group.

D. Intake of Dazomet

Intake of test article (mg/kg) was calculated at the same time at which food consumption was determined, using the following formula:

$$\frac{FA \times D}{BW_x}$$

FA = mean food consumption from day x-y to day x

D = dose in ppm

BW_x = body weight on day x

The group mean intake of Dazomet for male and female rats over the course of the study is summarized in the following table, with correction for actual amounts of test chemical intake as shown by analysis of test article concentration in food (12%, 14%, 13%, and 8% below nominal for the 5, 20, 80, and 320ppm dose levels, respectively):

TABLE 6

Group Mean Dietary Intake of Dazomet in Male and Female Rats Over 104 Weeks [a]

Dose Group (ppm)	Average Intake (weeks 0-104) (mg/kg/day) males	females
0	0	0
5	0.23	0.29
20	0.94	1.19
80	3.81	5.09
320	16.36	21.54

[a]data taken from Tables 041-050, pages 107-116 of registrant report.

It is noted that group mean intake of test article was 26-33% higher in female rats across all dose groups in comparison to male rats.

E. Clinical Signs and Pathology

Rats were individually monitored for signs of toxicity and pharmacologic effects once each day. Inspection and palpation were performed once a week in addition.

A summary of clinical observations for male and female rats (Tables 051-052, pages 117-118) was provided. There were no apparent observations which could be considered test article related, with the possible exception of increased incidence of palpable masses in male rats from the 80ppm dose group, and female rats from the 20 and 80ppm dose groups.

F. Ophthalmological Examination

Eyes in male and female rats from the 0 and 320ppm dose groups were examined prior to study initiation and after 24 months using a Heine Focalux hand-held slit lamp.

Results of these examinations (Figures 4.2.6.1 and 4.2.6.2, pages 50-51 of the report) showed no differences between treated and control rats of either sex.

G. Clinical Chemistry

a) Hematology

Blood was obtained from the retroorbital venous plexus for hematologic analysis from non-fasted rats. Collection and analysis of samples was conducted in random sequence (with the exception of differential blood count and reticulocyte measurement) at days 91-92, 183-184, 372-373, 554-555, and 722-723 after the start of test article administration. The following CHECKED parameters were measured using a particle counter (Coulter S Plus model, FRG):

_x_ total leucocyte count*	_-_ total plasma protein*
_x_ erythrocyte count*	_x_ leukocyte differential*
_x_ hemoglobin*	_x_ mean corpuscular HGB
_x_ hematocrit*	_x_ mean corpusc. HGB conc.
_x_ platelet count	_x_ mean corpusc. volume
_-_ packed cell volume	_x_ thromboplastin time
_-_ activated partial thromboplastin time	

*EPA guideline requirement "-" not examined

Leukocyte differential and reticulocytes were measured using an automatic differential system (Hematrak 480 model, FRG) or visually. Thromboplastin time was measured using a ball coagulometer (Amelung KC 10 model, FRG).

Significant changes in hematology occurring in male and female rats over the course of this study is summarized below (Table 7). It is noted that there were no apparent hematologic changes in male rats considered treatment-related over the course of this study. Thus, summary is made below for female rats only.

TABLE 7
Hematologic Alterations in Female Rats
from 104 Week Dietary Administration of Dazomet[a]

	Dose Groups females (ppm)				
	0	5	20	80	320
Hb - DAY 92 (mmol/L)	9.03±0.40	8.88±0.35	9.06±0.41	8.77±0.31	8.49±0.36[c]
DAY 184	9.12±0.33	8.97±0.47	9.11±0.25	9.07±0.30	8.56±0.39[c]
DAY 373	8.83±0.40	8.76±0.23	8.77±0.48	8.72±0.48	8.38±0.36[c]
DAY 555	8.36±0.53	8.29±0.22	8.38±0.61	8.26±0.31	7.99±0.38[b]
DAY 723	8.52±0.82	8.30±1.82	8.22±0.63	8.18±0.61	7.96±0.95
RBC-DAY 92 (tera/L)	7.88±0.42	7.63±0.42	7.76±0.44	7.53±0.30[b]	7.29±0.38[c]
DAY 184	8.52±0.38	8.35±0.53	8.41±0.23	8.38±0.33	7.94±0.44[c]
DAY 373	7.79±0.43	7.77±0.31	7.70±0.40	7.70±0.48	7.32±0.31[c]
DAY 555	7.24±0.46	7.14±0.21	7.07±0.39	7.11±0.35	6.89±0.34[c]
DAY 723	7.12±0.77	6.57±1.10	6.86±0.68	6.88±0.64	6.58±0.99

Table 7, cont.

	Dose Groups (females (ppm))				
	0	5	20	80	320
HCT- DAY 92 (fmol)	0.381±0.02	0.371±0.02	0.381±0.022	0.368±0.015	0.358±0.02[c]
DAY 184	0.415±0.02	0.409±0.024	0.414±0.013	0.412±0.012	0.390±0.022[c]
DAY 373	0.382±0.02	0.380±0.013	0.380±0.021	0.378±0.021	0.362±0.017[c]
PLT- DAY 92 (giga/L)	985±130	973±102	969±131	1026±82	1061±94
DAY 184	973±73	940±250	1018±109	1107±121[b]	1105±110[b]
DAY 373	948±95	983±140	977±140	1051±134[b]	1071±102[c]
DAY 555	950±81	998±177	981±108	1055±124[b]	1073±83[c]

[a]data taken from Tables 060-064, 126-130 of the report.
abbreviations used: Hb, hemoglobin; RBC, red blood cells; HCT, hematocrit; PLT, platelets

As shown above, significant decreases in plasma hemoglobin, red blood cells, and hematocrit were observed in female rats from the 80 and 320ppm dose groups over the course of this study. The most consistent effects were observed at the 320ppm dose level, where decreases in hemoglobin of between 5-6%, decreases in red blood cells of between 5-12%, and decreases in hematocrit of between 5-6% were observed during the course of the study. These decreases were found to be statistically significant in most cases. Platelets, in contrast, demonstrated an increase of between 7-13% for the duration of the study, also statistically significant over the course of the study. The significant changes observed in hematologic values for female rats as compared to males may be based upon the increased percentage intake of test article experienced by females in this study.

While the above changes are indicative of anemia, the registrant stated (page 55) that such process is likely a mild one, based upon the lack of changes in red blood cell characteristics and the lack of an increase in reticulocytes. Changes in platelet count in the 80 and 320ppm dose group of females is considered a treatment-related effect by the registrant (page 55).

b) Blood Chemistry

The following CHECKED parameters were measured at the same times as stated above for hematological deteminations:

_x_ glucose*
_x_ albumin*
_x_ globulin (calculated)
_x_ creatinine*
_x_ total bilirubin*
_-_ direct bilirubin
_-_ indirect bilirubin
_x_ urea nitrogen*
_x_ total protein*
_-_ uric acid

_x_ AST(SGPT)*
_x_ ALT(SGOT)*
_x_ alkaline phosphatase
_x_ serum cholinesterase
_-_ lactate dehydrogenase
_-_ sorbitol dehydrogenase
_-_ gamma glutamyl trans-peptidase

_x_ calcium*
_x_ phosphate*
_x_ sodium*
_x_ potassium*
_-_ phosphorous

_x_ triglycerides
_x_ cholesterol
_x_ chloride*

*EPA guideline requirement "-" not examined

Clinical chemistry parameters were determined using an automatic analyzer (Hitachi 737). In addition tc the above, serum triiodothyronine (T3) and thyroxine (T4) were also measured on study day 372-373 only using a photometer.

Significant observations made for blood proteins during the course of this study are summarized in the following table (Table 8). It is to be noted that female rats appeared to show more numerous changes than males, similar to that observed for hematologic changes as a result of test article administration.

TABLE 8
Changes in Blood Proteins in Male and Female Rats from
104 Week Dietary Administration of Dazomet[a]

	Dose Groups									
	males (ppm)					females (ppm)				
	0	5	20	80	320	0	5	20	80	320
protein-Day 91-92 (g/L)	62.64± 3.08	61.57± 4.42	61.77± 2.81	61.45± 3.62	59.62± 3.08	65.47± 4.60	62.67± 4.74	65.52± 3.88	59.90± 3.47[c]	57.69± 5.16[c]

Table 8, cont.

	males (ppm)					females (ppm)				
	0	5	20	80	320	0	5	20	80	320
protein-Day 372-373	66.49± 4.44	65.85± 4.10	66.56± 4.50	66.87± 3.26	64.41± 2.40	74.67± 4.77	75.40± 5.90	75.45± 4.15	71.87± 5.49	68.66± 4.41 [c]
protein-Day 554-555	65.36± 3.63	64.74± 5.66	64.83± 4.24	63.90± 3.01	63.61± 3.03	72.72± 5.05	73.29± 3.15	71.39± 5.56	69.17± 4.41	68.99± 4.80
albumin-Day 91-92 (g/L)	39.68± 2.35	39.14± 2.31	39.33± 2.46	39.12± 2.22	38.64± 2.47	43.71± 2.75	42.68± 2.95	44.15± 2.65	40.92± 1.82 [c]	39.97± 3.08 [c]
albumin-Day 372-373	37.69± 1.83	37.33± 2.25	37.79± 2.43	37.24± 2.63	37.56± 1.61	44.82± 2.88	45.72± 3.45	45.78± 2.81	43.66± 3.51	41.74± 2.15 [c]
globulins-Day 91-92 (g/L)	22.98± 3.10	22.43± 3.71	22.44± 2.61	22.32± 3.37	20.98± 3.64	21.76± 2.77	19.99± 2.58	21.37± 1.84	18.98± 2.13 [c]	17.72± 2.61 [c]
globulins Day 183-184	29.61± 2.56	30.46± 2.73	29.32± 1.86	30.60± 2.70	27.79± 1.69	28.39± 2.27	27.99± 1.93	28.25± 2.05	26.84± 1.98	25.95± 2.71 [c]
globulins Day 372-373	29.00± 3.80	28.52± 3.31	28.77± 2.88	29.63± 2.78	26.84± 1.97	29.85± 2.54	29.68± 4.44	29.66± 3.01	28.21± 2.62	26.92± 3.29 [b]

[a] data taken from Tables 140-154, pages 206-220 of the report.

[b] $p < 0.05$ vs control; [c] $p < 0.01$ vs control.

Female rats experienced significant decreases in serum total protein, albumin, and globulins over the course of this study, while changes in blood proteins in male rats were not significantly altered at any dose of test article. On day 91-92 of the study, serum total protein in female rats was decreased 8.5 and 11% at the 80 and 320ppm dose levels vs control. A similar decrease of 8% was also observed on day 372-373 for female rats in the 320ppm dose group. Although a significant decrease was observed at day 554-555 for serum total protein in female rats, this decrease was

small (5%).

Serum albumin showed a decrease of 6 and 8.5% in female rats from the 80 and 320ppm dose groups on day 91-92. Serum globulins were decreased in female rats on day 91-92 by 13 and 18% in the 80 and 320ppm dose groups, and by 8 and 10% in the 320ppm dose group on study days 183-184 and 372-373, respectively.

Changes in serum cholesterol in male rats and changes in blood urea and creatinine in female rats is summarized below (Table 9):

TABLE 9

Changes in Cholesterol in Male Rats and Changes in Urea and Creatinine in Female Rats 104 Week Dietary Administration of Dazomet[a]

	Males (ppm)				
	0	5	20	80	320
cholesterol (mmol/l)					
Day 183	2.32±0.41	2.55±0.49	2.59±0.55	2.80±0.53[b]	2.94±0.39[c]
Day 372	2.88±0.46	3.21±1.27	3.05±0.76	3.62±1.86	3.49±0.59
Day 554	3.32±0.50	3.91±1.29	3.84±1.20	3.63±0.60	4.03±0.91
Day 722	3.88±0.70	5.15±1.70[b]	4.99±1.61	4.11±1.06	4.80±0.87
	Females (ppm)				
	0	5	20	80	320
creatinine (µmol/l)					
Day 92	56.73±8.31	52.66±5.19	54.06±4.96	50.89±4.60[c]	50.02±4.97[c]
Day 373	53.02±5.73	53.86±3.92	53.18±4.73	51.82±4.76	49.03±4.01[b]
Day 723	49.70±3.93	47.21±3.96	45.96±2.89[b]	46.92±5.43	45.21±3.08[c]

Table 9, cont.

	Females (ppm)				
	0	5	20	80	320
urea (mmol/l)					
Day 373	6.79±0.85	5.89±0.8[b]	5.93±1.08	5.92±1.21	5.39±1.40[c]
Day 555	7.18±1.06	6.23±0.86[c]	6.72±0.81	6.43±1.18[b]	6.36±0.71[b]
Day 723	7.46±1.68	6.36±1.17[b]	6.16±0.58[c]	6.64±1.31	6.25±0.64[b]

[a]data taken from Tables 140-154, pages 206-220 of the report.

[b] $p < 0.05$ vs control; [c] $p < 0.01$ vs control.

On day 91, serum cholesterol was increased 20 ($p < 0.05$) and 26% ($p < 0.01$) in male rats from the 80 and 320ppm dose groups. Although not found statistically significant, increases of between 20-32% were observed in cholesterol in male rats from the 320ppm dose group on days 372, 554, and 722.

In female rats, cholesterol was significantly affected only on day 184, where an increase of 24% was observed in rats from the 320ppm dose group. However, serum urea and creatinine were significantly decreased on study days 92, 373, and 723 for creatinine and days 373, 555, and 723 for urea. Decreases in creatinine were between 7-10% at the 320ppm dose level, while decreases in urea were 11-20% at the 320ppm dose level. Significant decreases in urea were also observed at the 5 and 80ppm dose level on days 555 and 723, indicating that the effect observed at the 320ppm dose level on day 373 might be affecting rats at the lower doses later in the study.

Other instances of changes in clinical chemistry which occurred during this study were: A significant (38 and 50%) increase in bilirubin levels in female rats at the 320ppm dose level on study days 373 and 555; a significant decrease in triglycerides of 30 and 40% at the 80 and 320ppm dose levels in female rats on study day 92.

c) Enzymes

In male rats, an apparent dose-related decrease in serum alkaline phosphatase activity was observed on day 91 of the study which became statistically significant at the 320ppm dose level, where activity was decreased by 14% vs control. Serum cholinesterase was also decreased in a dose-dependent manner on this study day, although no changes achieved statistical significance. At subsequent measurement times, no significant changes in serum enzymes were observed in male rats.

In female rats, serum cholinesterase was decreased on day 92 in the 80ppm dose group and on days 92, 184, and 373 in the 320ppm dose group. At 92 days, activity in rats from the 80ppm dose

group was decreased by 14% ($p < 0.05$), while activity in rats from the 320ppm dose group was decreased by 35% ($p < 0.01$). Activity of cholinesterase at 184 days was decreased 27% vs control in the 320ppm dose group ($p < 0.01$), and decreased 28% vs control in the 320ppm dose group on day 373. On day 373, activity of alkaline phosphatase was decreased 18 and 20% ($p < 0.05$) in female rats from the 80 and 320ppm dose groups, respectively. No significant changes were observed in enzyme activity on measurement days 555 and 723 in female rats.

H. Urinalysis: (Tables 157-166, pages 223-232 of the report; keys on pages 412-413)

Urine was collected overnight from surviving rats on study days 85-86, 176-177, 365-366, 547-548, and 715-716. The following parameters were measured:

- appearance	x glucose
- volume	x pH
- specific gravity	x bilirubin
x protein	x urobilinogen
x ketone	x nitrite
x blood	- color
x sediment	- total reducing substances

Urine constituents were measured semi-quantitatively using test strips (Combur-9-test RL, Boehringer, FRG) and a reflection photometer (Urotron RL9 model). At the 85-86 day collection point, a Clini-Tek (AMES, FRG) reflection photometer was used. Sediment was evaluated microscopically.

No significant effects of test article treatment were reported upon analysis of urine from male and female rats at all dose levels.

I. Organ Weights

The weight of the liver, kidneys, adrenal glands, brain, and testes was determined in all rats killed on schedule.

Absolute and relative organ weight data were summarized by the registrant on pages 995-998. In male rats, the absolute weight of the kidneys was significantly decreased in the 320ppm dose group vs control, from 4.26±0.41g to 3.84±0.39g, a decrease of 10% ($p < 0.05$). No other changes in absolute organ weight were observed in male rats. In female rats, a similar decrease in absolute kidney weight was observed, from 2.88±0.43g in controls to 2.46±0.21 g in the 320ppm dose group a decrease of 14% ($p < 0.05$). No other organ weights were significantly affected in female rats.

The relative weight of the brain and liver were significantly increased in male rats from the

320ppm dose group. Relative brain weight increased from 0.30±0.05g in control males to 0.34±0.05g in males from the 320ppm dose group, an increase of 13% ($p < 0.05$). Relative liver weight increased from 2.73±0.31 in control males to 3.48±0.38 in males from the 320ppm dose group, an increase of 27% ($p < 0.05$). No changes in relative organ weights were observed in female rats at study termination.

J. Macroscopic Observations

All rats surviving to the end of the study as well as those dying or killed during the study were killed by decapitation under carbon dioxide anesthesia. All organs were examined and all macroscopic findings recorded at necropsy.

Summaries of macroscopic findings are presented in tabular form on pages 1001-1030. Examination of these data shows that in male rats, lung foci (1 in the 5ppm dose group, 3 in the 20ppm dose group, and 4 in the 320ppm dose group) were increased, as was retraction of the kidney (observed in 3 rats from the 320ppm dose group only) and masses in the pituitary (incidence in the 0, 5, 20, 80, and 320ppm dose groups: 2, 4, 6, 5, and 6 rats).

In female rats, masses in the ovaries were increased in incidence in rats from the 5 and 320ppm dose groups (3 rats and 5 rats respectively, vs 1 rat in control). In addition, adrenal masses were increased in incidence in rats from the 20, 80, and 320ppm dose groups (4, 2, and 3 rats respectively, vs 0 rats in control group) as was cysts in the liver (0 in control rats, and 2, 3, 2, and 4 in the 5, 20, 80, and 320ppm dose groups, respectively).

K. Microscopic Observations

The following tissues were removed and preserved in 4% formaldehyde solution (page 974) :

Digestive

- tongue
x salivary glands*
x esophagus*
x stomach*
x duodenum*
x jejunum*
x ileum*
x cecum*
x colon*
- rectum*
x liver*
x pancreas*
x gall bladder*

Respiratory

x trachea*
x lungs*
- nasal cavity

Cardiovascular

x aorta*
x heart*
x bone marrow*
x lymph nodes*
x spleen*
x thymus*

Urogenital

x kidneys*
x urinary bladder*
x testes*
x epididymides*
x seminal vesicle*
x prostate
x ovaries*
x uterus*
- vagina

(cont.)

Neurologic	Glandular	Other
x brain*	x adrenals*	x bone (femur)*
x peripheral nerve*	- lacrimal gland	x skeletal muscle*
x spinal cord (3 levels)*	x mammary gland*	x skin*
x pituitary*	x parathyroids*	x all gross lesions*
x eyes*	x thyroids*	

*OECD guideline requirement "-" not examined

Tissues listed above were trimmed, processed, and embedded in paraffin wax. Hematoxylin and eosin stain was applied to sections of all tissues from rats in control and high dose groups, and to tissues from rats in the low and mid dose groups that died or were killed in extremis. The remainder of rats in the low and mid dose groups received microscopic examination of only the lungs, liver, spleen, kidneys, and all gross lesions.

In addition to H & E stain, frozen sections of the liver of all rats was stained with oil red O, for detection of fat, and the spleen stained additionally with Prussian blue for detection of iron.

1) Neoplastic Observations

Data on neoplastic lesions were provided in several formats by the registrant. In one format, data from all rats were presented (pages 1046-1053); in others, data were divided into lesions observed only in those rats surviving to study termination (pages 1054-1061) and lesions observed in those rats killed during the study (pages 1062-1069). A general evaluation of rats with neoplasms was provided (pages 1072-1080) as well as a listing of neoplasms and metastases according to animal number (pages 1081-1096). Review of these data indicated that in large part, there did not appear to be any significant effects of test article administration on neoplastic development in male or female rats. This is slightly in contrast to the results observed from study # 70C0318/8584, in which an apparent increase in the incidence of malignant lymphoma in male rats dosed at 80ppm and mammary gland fibroadenoma and adenocarcinoma in female rats dosed at 80ppm was observed.

2) Non-Neoplastic Observations

Data provided by the registrant on non-neoplastic lesions (beginning on page 1032) in this study were given in a similar format as that for neoplastic lesions (see above, neoplastic observations).

The registrant stated (page 979 of the report) that non-neoplastic lesions between control and treated rats were not remarkable, with the following exceptions:

a) hepatocellular fat deposition (zone 1): observed in 13/20 female control rats and 20/20

female high dose rats (incidence in 5, 20, and 80ppm dose levels was 11/20, 13/20, and 12/20, respectively). **Note** : the incidence of this lesion in control rats was higher than that found in control rats from study 70C0318/8584.

b) **hepatocellular vacuolation**: observed in female rats with zero incidence except at the 320ppm dose level, where the incidence was 5/20 rats.

c) **altered cell foci**: observed in female rats with the following incidence (3/20 in controls; 1/20 at the 5ppm dose level; 3/20 at the 20 and 80ppm dose levels; 7/20 at the 320ppm dose level).

It is to be noted that the non-neoplastic lesions noted in this study are those also noted in study # 70C0318/8584.

III. DISCUSSION

In the present study, male and female rats were administered dazomet in the diet for 104 weeks at levels of 0, 5ppm (0.23 mg/kg/day males; 0.29 mg/kg/day females), 20ppm (0.94 mg/kg/day males; 1.19 mg/kg/day females), 80 ppm (3.81 mg/kg/day males; 5.09 mg/kg/day females), and 320 ppm (16.36 mg/kg/day males; 21.54 mg/kg/day females) in order to determine the toxic effects from chronic administration of this chemical. Neoplastic and non-neoplastic lesions resulting from administration of dazomet were also assessed at study termination. Rats were monitored for treatment related effects on mortality, body weight gain, food consumption, palpable masses, and clinical signs of toxicity. Measurements for alterations in hematology, clinical chemistry, and urinary constituents were made periodically during the study.

No significant effects on mortality were observed from administration of dazomet in this study in male or female rats. Significant signs of clinical toxicity were not apparent at any dose level over the course of this study. However, body weight and body weight gain were affected in both male and female rats, primarily at the 320ppm dose level. Group mean body weight in male rats from the 320ppm dose group was decreased slightly (4%) during the whole study, but terminal body weight was found to be 13% below the control value. In female rats from the 320ppm dose group, group mean body weight was decreased 7-8% from days 14-63 of the study, but recovered to levels close to the controls. Terminal body weight in female rats from the 320ppm dose group was decreased by 9% compared to controls at study termination. Group mean body weight gain for weeks 0-13 of the study was decreased 9% in male rats and 11% in female rats from the 320ppm dose group. Overall group mean body weight gain (weeks 0-104 of the study) was decreased 16% in male rats and 13% in female rats from the 320ppm dose group.

Food consumption was not decreased in either male or female rats at any dose level during this study. In fact, significant increases in food consumption were observed in male rats from the 5, 20, and 80ppm dose groups at week 13, and in female rats from all dose groups at week 13 of the study. Overall food efficiency for weeks 1-13 of the study was not significantly affected in male rats, but a 16% decrease in overall food efficiency was observed in female rats from the 320ppm dose group. It is to be noted that intake of dazomet was greater in female rats by 26-33% than male rats at all dose levels tested (Table 6, page 11 of DER). This greater intake could explain the apparent greater sensitivity of female rats to the toxic effects of dazomet administration.

Hematologic effects were observed to a large extent in female rats from the 80 and 320ppm dose groups over the course of this study, and included significant decreases in red blood cells, hemoglobin, and hematocrit. In conjunction with this, a significant increase in platelets was observed at the 80 and 320ppm dose groups over the course of the study. This platelet increase was also observed in male rats over the duration of the study, but was not statistically significant. These hematologic changes are indicative of an anemic process, and the greater hematologic effects observed in female rats is likely a reflection of greater test article intake in this sex.

Similar to that observed in the subchronic rat study with dazomet (# 30C0318/8544), significant decreases in serum albumin, total protein, and globulins were observed in female rats at the 80 and 320ppm dose groups. The registrant stated (page 54 of the report) that these decreases, along with the decreased triglyceride also observed in female rats is related to liver toxicity of dazomet, although no specific pathology was identified in the present study to support this claim. Nonetheless, the changes in blood proteins and triglycerides are regarded as treatment related, possibly related to unspecified liver toxicity. Changes in serum urea and creatinine, although significantly decreased in female rats over the course of the study, were not regarded as treatment related, although this may also be related to apparent liver toxicity. Male rats did not show such extensive alterations in serum chemistry over the course of this study, with the exception of a significant increase in serum cholesterol of between 20-32%.

Changes in enzyme activities measured in serum were observed in both male and female rats, but effects in female rats were more lasting. Males showed a decreased alkaline phosphatase activity of 14% in the 320ppm dose group on day 91, as well as a similar decrease in cholinesterase activity. However, no changes were observed subsequent to this time in male rats. Female rats in contrast showed significant (14-28%) decreases in serum cholinesterase from days 92-373 of the study at the 80 and 320ppm dose levels. The significance of this is unclear, since no clinical signs related to cholinergic toxicity were observed in female rats.

The incidence of foci in lungs, retraction of the kidneys, and pituitary masses of male rats was slightly increased at the 320ppm dose level in comparison to controls, as was the incidence of ovarian and adrenal masses and cysts in the liver in female rats at this same dose. These effects may be considered treatment related, but preclude definite association with test article administration, as the increases are not dramatic.

There was no significant effect of test article administration on tumor formation in male and female rats at any dose tested in this study. This result is in slight contrat to results obtained from the rat carcinogenicity study with dazomet, in which an apparent increase in the number of male and female rats at the 80ppm dose level with malignant lymphoma, and an increase in the number of female rats with mammary gland fibroadenoma and adenocarcinoma at the 80ppm dose level was noted. However, as the differences were not statistically significant in the carcinogenicity study, they may represent variation in these tumor types within this strain of rat from this laboratory.

Certain non-neoplastic lesions were found to be increased in treated male and female rats. Specifically, diffuse hepatocellular fat deposition and hepatocellular vacuolation were observed in increased incidence in female rats in the 320ppm dose group in comparison to control. In addition, altered cell foci were observed in increased incidence in female rats from the 320ppm dose group. These findings corroborate those observed in the carcinogenicity study with dazomet in rats, although male rats in that study were also observed with liver fat deposition, in contrast to the present study. These are considered test article related by the registrant and the reviewer.

The following information is requested:

1) Explanation of the switch from one type of refraction photometer to another during the study for measurement of urinary constituents is requested.

IV. CONCLUSIONS

Technical Dazomet was administered to male and female rats in the diet for 104 weeks at doses of 0, 5ppm (0.23 mg/kg/day males; 0.29 mg/kg/day females), 20ppm (0.94 mg/kg/day males; 1.19 mg/kg/day females), 80 ppm (3.81 mg/kg/day males; 5.09 mg/kg/day females), and 320 ppm (16.36 mg/kg/day males; 21.54 mg/kg/day females) in order to determine the toxic effects from chronic administration of this chemical. Reduced group mean body weight and body weight gain was observed in male and female rats at the 320ppm dose level. Significant decreases in hematologic parameters (red blood cells, hemoglobin, hematocrit) were observed in female rats at the 80 and 320ppm dose level, as were significant decreases in serum albumin, total protein, and globulins, and a significant increase in platelets at 80 and 320ppm dazomet. Male rats showed slight increases in platelets at the 320ppm dose level and a significant increase in serum cholesterol at the 80 and 320ppm dose levels. Relative liver : body weight was also increased in male rats at the 320ppm dose level, but no significant organ weight increases were observed in female rats.

The No Observed Effect Level (NOEL) = 20 ppm

The Lowest Observed Effect Level (LEL) = 80 ppm (decrease in serum albumin, globulins, total protein, hemoglobin, hematocrit, and red blood cells in female rats; increased serum cholesterol in male rats).

V. CLASSIFICATION
Core Guideline

This study satisfies the guideline requirements (83-2) for a chronic toxicity study in rats.

Dazomet

Page____ is not included in this copy.

Pages 63 through 65 are not included.

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 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.

Reviewed by: Timothy F. McMahon, Ph.D.
Section I, Toxicology Branch II (H7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. 10/16/91
Section I, Toxicology Branch II (H7509C)

Data Evaluation Report

Study type: Chronic oral toxicity - dogs
Guideline: 83-1

EPA ID Numbers: MRID number: 419677-01
Caswell No: 840
HED Project Nos: 1-1996

Test material: Dazomet

Synonyms: tetrahydro-3,5-dimethyl-2 H-1,3,5-thiadiazine-2-thione

Study number(s): 33DO318/85118

Title of report: Report on the Study of the Toxicity of Dazomet in Beagle Dogs Via the Diet Over 12 Months.

Testing Facilities: BASF Aktiengesellschaft
Department of Toxicology
D-6700 Ludwigshafen
W. Germany

Sponsor: BASF Corporation
Agricultural Chemicals Group
Research Triangle Park, N.C. 27709

Author(s): Dr. Hellwig

Study Completed: February 1989

Conclusions: Dazomet was administered to male and female beagle dogs at dose levels of 0, 15ppm (0.28 mg/kg/day, males; 0.35 mg/kg/day, females), 50ppm (1.05 mg/kg/day, males; 1.12 mg/kg/day, females), and 150ppm (3.15 mg/kg/day, males; 3.50 mg/kg/day, females). Toxicity in female dogs was evident at 50 and 150ppm dazomet, and included increased liver : body weight ratio, increased serum alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase activities, decreased serum albumin, discoloration of the liver parenchyma, increased severity of iron positive pigment deposition in the liver, and chronic active hepatitis. Toxicity in male dogs was limited to one dog at the 150ppm dose level, who showed decreased body weight gain and similar signs as those mentioned above for female dogs.

Systemic NOEL = 15 ppm (females); = 50 ppm (males)
Systemic LEL = 50 ppm (females; increased liver : body weight ratio)
= 150 ppm (males; decreased body weight gain; hematological effects)

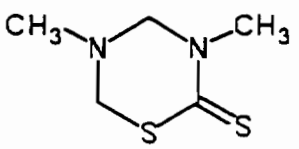
Classification: Core minimum

This study satisfies the guideline requirements (83-1) for a chronic oral toxicity study in dogs.

I. MATERIALS AND METHODS

A. Test Material: Dazomet, test substance # 85/318
batch # 26-5297
average purity: 98.2% (page 22 of report)
description: solid

Structure:



B. Vehicle: dietary preparation

C. Test Animals: Species: beagle dog, male and female
Source: unclear; stated as "BASF breed" (page 23).
Age: approximately 7-9 months.
Weight (range): males, 9.4-12.0kg (mean: 10.7kg); females, 8.2-11.7kg (mean: 9.6kg).

D. Animal Husbandry:

Twenty-four male and 24 female dogs were used in this study. Dogs were stated to be free from any signs of disease when transferred from the breeding section. Vaccination for distemper, hepatitis, leptospirosis, and parvovirus as well as deworming was performed at regular intervals. Dogs were allowed 7 days acclimation to the laboratory environment before treatment. Dogs were housed in pairs in kennels measuring approximately 9 m^2 floor space. Lighting corresponded to the natural day/night rhythm, and dogs had constant access to the outside portion of the kennel except during feeding (one hour daily).

Food (dog maintenance KILBA laboratory diet) mixed with test substance was offered daily as 350g ground feed mixed with 350ml drinking water. Mixes were made immediately before feeding, and the entire feeding procedure was completed within one hour. One dog was kept in the outside kennel and one dog in the inside kennel during feeding. When bowls were removed, food not eaten was weighed and subtracted from the total food offered.

E. Experimental Design and Dosing:

Animals were assigned to pens according to a computer program designed to ensure homogenous body weights among treatment groups.

Six dogs per sex per dose were used. Test groups included control and the following dose groups:

Group #	Dose (ppm)	Animal #s male	female
0	0	207:6, 195:6, 151:6, 197:6, 229:6, 177:6	196:6, 240:6, 242:6, 152:6, 168:6, 222:6
1	15	211:6, 193:6, 135:6, 163:6, 205:6, 231:6	186:6, 238:6, 154:6, 246:6, 190:6, 204:6
2	50	183:6, 209:6, 189:6, 215:6, 179:6, 219:6	162:6, 188:6, 156:6, 166:6, 172:6, 174:6
3	150	149:6, 203:6, 201:6, 161:6, 141:6, 225:6	150:6, 234:6, 178:6, 200:6, 206:6, 176:6

Dose selection for this study was based upon preliminary studies of capsule and dietary administration to beagle dogs. Capsule administration at doses of 320 and 80 mg/kg resulted in rank toxicity (unsteady gait and progressive weakness of the hindlimbs) and severe vomiting, wi at a dose of 20 mg/kg few signs were observed. Dietary administration at doses of 12,000, 3,000. and 750ppm resulted in vomiting at all dose levels and considerable loss of body weight. Dogs in his first dietary study were returned to normal feed for 9 days and then used for a second test eedir.g at doses of 200, 400, and 600ppm test material. At these doses, test material was apparently well tolerated by the dogs. Vomiting occurred only during the first 2 days of administration, and clinical signs consisted of changes in red cell count at 600ppm, and in some dogs at 400ppm. Possible kidney dysfunction in the form of increased urea was observed in one female dog at 600ppm. In a subchronic toxicity study (# 87-0456-0001), dazomet administration a evels of 25, 100, and 400/200ppm resulted in increased liver:body weight ratios and hemosider n male and female dogs at the 400/200ppm dose level.

Based on these findings, 150ppm was selected as the high dose for the present study, and was expected to result in toxic effects.

F. Dietary Preparation and Analysis:

Dazomet was incorporated into ground diet at the required concentrations by preparation of a p nix in which test substance was "intensely" mixed with a small portion of feed in a beaker using a spatula. Premix was prepared from this by using a Bosch mixer. The premix was then adjusted to he desired concentration with the appropriate amount of feed using a GEBR.LODIGE laboratory nixer. Test diets were prepared twice each week , stored at 4 °C after mixing, and removed from storage only shortly before preparation of the paste for consumption. It was not stated whether the concentration of dazomet was adjusted for body weight gain during the study.

Stability of dazomet was determined prior to study initiation (98.2%) and again at study ermination (98.2%), and was found to be stable over the study period (page 44 of report). Test di were analyzed for stability and homogeneity of dazomet in food prior to study initiation, approximately 6 weeks after study initiation, and again at study termination (pages 849-859 of the eport). Results demonstrated that stability and homogeneity at all dose levels did not vary significantly from target values over the course of the study. However, it is to be noted that in the

determination of stability of dazomet in the feed mix, concentration of dazomet appeared to decline with time. Using an average value of 13.8 mg/kg (page 849 of the report) for concentration of dazomet in food at the 15 mg/kg dose level, at 15 minutes room temperature, the concentration of dazomet had declined to a mean value of 12.3 mg/kg (89% of zero time value). At 30 minutes room temperature, the concentration of dazomet declined to 11.1 mg/kg (80% of zero time), while at one hour, a value of 9.7 mg/kg (70% of zero time value) was obtained.

Note: Analysis of dietary concentration of dazomet over the course of this study (pages 852-855 showed concentrations of test material which were in an acceptable range in comparison to target values. However, the apparent instability of test material after mixing of the feed mixtures with water indicates that dogs did not receive the stated intake of dazomet for the one hour feeding period. As it appears that after one hour, concentration of test article was decreased to approximately 70% of the zero time value, this factor will be used in calculating intake of dazomet at all dose levels.

G. Statistical Analysis:

A copy of the statistical procedures used in this study is attached to this review.

H. Compliance:

A signed statement of "GLP Statement of Compliance" was provided. This study was conducted according to the OECD Principles of Good Laboratory Practice.

A signed " Data Confidentiality Claim" statement was provided.

A signed "Statement of the "Quality Assurance Unit" was provided.

A signed statement of EPA Flagging Criteria was provided.

II. OBSERVATIONS AND RESULTS:

1) **Mortality** : All dogs were checked twice daily for moribund appearance or mortality. Observations were made once a day on weekends and holidays.

No mortality was reported during the study period.

2) **Clinical Observations** : All dogs were checked for evident signs of toxicity at least once a day on workdays. If signs were observed, dogs were observed several times daily.

Clinical signs were observed in some female dogs in this study. One female dog from the 50ppm dose group was observed with diarrhea on study day 253. One female dog in the 150ppm dose group vomited on day 184 of the study, while another dog in this dose group was found to be emaciated from study day 267 until study termination.

The emaciation observed in one female dog was considered treatment-related, while the diarrh and vomiting were considered incidental and not treatment-related.

3) **Body Weight**: Body weight data were collected for all dogs 7 days prior to study initiation ar

then weekly thereafter. Group mean body weights and body weight gains in male and female dogs are summarized in the following Table:

TABLE 1
Group Mean Body Weights (in Kg) in Male and Female Dogs from 52 Week Oral Administration of Dazomet[a]

	Dose Groups							
	males (ppm)				females (ppm)			
Days on Test	0	15	50	150	0	15	50	150
0	10.7	10.7	10.7	10.7	9.5	9.6	9.6	9.6
7	10.8	10.8	10.7	10.8	9.6	9.6	9.6	9.6
35 (36)	11.1	11.1	11.2	11.1	9.9	9.8	9.7	9.6
92 (91)	11.7	12.0	11.9	11.8	10.5	10.3	10.5	10.3
182	12.2	12.7	12.4	12.2	11.1	10.8	11.2	11.1
364	12.0	12.2	11.9	11.6	10.8	10.3	10.8	10.4

Data from Tables 095-108, pages 159-173 of registrant report, N=6. Values in parentheses represent days on which female dogs were weighed.

No significant changes were observed in group mean absolute body weight in male or female dogs from any test group over the course of this study.

Group mean body weight gain over the course of the study at selected times is summarized below (Table 2):

TABLE 2
Group Mean Body Weight Gain (in Kg) in Male and Female Dogs from 52 Week Oral Administration of Dazomet[a]

	Dose Groups							
	males (ppm)				females (ppm)			
Days on Test	0	15	50	150	0	15	50	150
0-91 (92)	1.0	1.3	1.2	1.1	1.0	0.7	0.9	0.7
% control	—	130	120	110	—	70	90	70
0-182	1.5	2.0	1.7	1.4	1.6	1.2	1.6	1.5
% control	—	133	113	93	—	75	100	93
0-364	1.4	1.6	1.3	0.8	1.3	0.8	1.2	0.8
% control	—	123	100	61	—	61	92	61

Data from Tables 109-122, pages 173-186 of registrant report, N=6. values in parentheses denote days on which female dogs were weighed.

Body weight gain in treated male dogs did not appear to be significantly affected for days 0-91 of the study, but was decreased for the study duration (days 0-364) in dogs from the 150 ppm dose group. This decrease in body weight gain in male dogs at the 150ppm dose group was the result of an individual dog in this dose group (dog 141:6), which showed weight loss from day 196 of the study. Thus, it can be considered that treatment with test article affected this one dog (as there was also significant liver pathology and altered clinical chemistry parameters in this dog).

Body weight gain in female dogs, in contrast to male dogs, was not significantly affected at any dose level. Although apparent decreases in body weight gain are observed in Table 2, there is no dose-related effect, and no treatment related effect on absolute body weight was observed (Table of DER).

Food Consumption: Food consumption was recorded daily for for male and female dogs. od not consumed was weighed and subtracted from the initial amount of food offered. Food iciency was calculated on a monthly basis for each test group using the following formula:

$$\frac{BW_{x+n} - BX_x}{F_y}$$

V_{x+n} = mean body weight on day x+ 28 (kg)

V_x = mean body weight on day x (kg)

= mean food consumption from days 0-27, 28-55, etc. divided by 2. Food consumption was vided by 2 because half of the feed ration consisted of water.

od consumption in male dogs (Table 001-047, pages 65-111 of the report) was not significantly fected over the course of the study. In female dogs, food consumption appeared to be affected ring the first 20 days of the study in the 150ppm dose group, due to an apparent decrease in food nsumption for 3 of the 6 dogs (#'s 150:6, 200:6, and 206:6). Dog # 206:6 continued to show creased food intake for the remainder of the study. The varying degree of food intake for the dogs the other dose groups was not considered treatment related by the registrant.

od efficiency for the first approximately 90 days of the study was not apparently different among e various treatment groups of male and female dogs (Tables 123-124, page 187 of the report). owever, for the study duration (days 0-363), food efficiency was decreased from 1.0 in control ale dogs to 0.7 at the 150ppm dose level. In female dogs, food efficiency for the study period 0-3 days was decreased from 1.0 in the control group to 0.6 in the 15 and 150ppm dose groups. e registrant stated (page 51) that these changes were not considered substance related.

he reported patterns of food consumption and body weight gain in male dogs does not appear to test article related. In female dogs, the reported patterns of body weight and food consumption ow that there is a possible test article related effect at the 50 and 150ppm dose level. Although creased food efficiency and body weight gain was also observed at the 15ppm dose level in male dogs, pathologic and clinical chemistry changes observed at the 150ppm dose level indicat st article related toxicity.

Intake of Dazomet: Test article intake was determined at the same times as body weight. he group mean intake of dazomet for male and female dogs over the course of the study is mmarized in the following table, with correction for the decomposition of test article to 70% of minal after one hour at room temperature (page 5 of DER).

TABLE 3

Group Mean Dietary Intake of Dazomet in Male and Female Dogs Over 104 Weeks[a]

›se oup (ppm)	Average Intake (days 0-104) (mg/kg/day) males	females
0	0	0
15	0.28	0.35
50	1.05	1.12
50	3.15	3.50

ata taken from Tables 125-138, pages 188-201 of registrant report.

s noted that for the study duration, test article intake was higher in female dogs by 25, 6, and 11% the 15, 50, and 150ppm dose levels.

Ophthalmologic Examination: Ophthalmoscopic examination was performed on all dogs or to the start of treatment and again at the end of the study using a KOWA-RC 2 fundus camera.

esults, as summarized in Table 140, page 203 of the report, showed no ocular abnormalities in y dog during the conduct of this study.

Clinical Pathology: Blood samples were obtained from the vena cephalica antebrachii of a gs 3 days before test article administration, and again at 95, 186, and 366 or 368 days after stuc tiation. Blood samples were analyzed in random sequence except for the differential blood coun d reticulocytes. At study termination, dogs were weighed, anesthetized and sacrificed by sanguination from the cervical and brachial vessels. Absolute and relative weights of the liver, dney, thyroid, adrenal glands, brain, testes, and ovaries were determined. Tissue samples were eserved in 4% formaldehyde solution, followed by histochemical processing (H&E stain) and amination by light microscopy. Liver, spleen, and kidneys from all dogs were stained additionall th Pearl's Prussian blue.

Hematology: The following CHECKED parameters were measured:

x total leucocyte count*	x total plasma protein*
x erythrocyte count*	x leukocyte differential*
x hemoglobin*	x mean corpuscular HGB
x hematocrit*	x mean corpusc. HGB conc.
x platelet count	x mean corpusc. volume
- packed cell volume	- prothrombin time
x activated partial thromboplastin time	

PA guideline requirement "-" not examined

Hematological measurements were made using an S Plus model particle counter (Coulter, FRG), while differential blood counts were performed using an automatic differential counter (Hematrak 480 model) or visually. Reticulocytes were counted visually. Clotting analysis was carried out using a ball coagulometer (Amelung KC 10 model).

Hematologic data were provided in Tables 141-148, pages 204-211 of the report. There were no reported alterations in hematologic parameters in male and female dogs related to administration o test article, with the exception of one male dog from the 150ppm dose group who showed decreased values for erythrocytes (4.49 vs 6.73 in controls), hemoglobin (6.68 vs 10.23 in controls) and hematocrit (0.317 vs 0.476 in controls) at day 366 of the study.

b) Blood Chemistry: The following CHECKED parameters were measured using an automatic analyzer (Hitachi 737, Boehringer, FRG):

_x_ glucose*	_x_ AST(SGPT)*
_x_ albumin*	_x_ ALT(SGOT)*
_x_ globulin (calculated)	_x_ alkaline phosphatase
_x_ creatinine*	_-_ creatine phosphokinase
_x_ total bilirubin*	_-_ lactate dehydrogenase
_-_ direct bilirubin	_-_ sorbitol dehydrogenase
_-_ indirect bilirubin	_-_ gamma glutamyl trans-peptidase
_x_ urea nitrogen*	
_x_ total protein*	
_-_ uric acid	
_x_ calcium*	_x_ triglycerides
_x_ phosphate*	_x_ cholesterol
_x_ sodium*	_x_ chloride*
_x_ potassium*	
_x_ phosphorous	

*EPA guideline requirement "-" not examined

In male dogs, there were no reported group mean clinical chemistry values indicative of a treatment related effect; however, one dog (# 141:6) showed dramatically elevated values for alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase on those study days (95, 186, and 366) on which enzymes were measured. In addition, this dog showed increase total bilirubin on days 186 and 366, increased globulin on day 366, and a decrease in serum albumin on day 366.

In female dogs, treatment related effects on enzyme activities were apparent in two dogs from the 150ppm dose group (#'s 178:6 and 206:6). A progressive increase in values for alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase were observed over the course of the study, such that by the end of treatment, group mean alanine aminotransferase was elevated almost 300%, aspartate aminotransferase 45%, and alkaline phosphatase 101% in comparison to controls. Significant decreases in serum albumin were also observed on days 35

and 366 in female dogs from the 150ppm dose group. On day 95, group mean albumin was decreased from 37.91 in controls to 34.95 in the 150ppm dose group ($p < 0.01$). A similar observation was reported on day 368. In contrast to the findings for serum enzymes, the decrease in serum albumin appeared to be the result of a general decrease in this dose group and was not confined to specific dogs.

8) **Urinalysis:**

Collection of urine for urinalysis was conducted 5 days prior to test article administration in all animals, and again on days 92-93, 184, and 366 or 368 of the study. Urine was collected overnight in metabolic cages after the animals received approximately 500ml drinking water. The following CHECKED parameters were measured:

_x_ appearance	_x_ glucose
_x_ volume	_x_ pH
_x_ specific gravity	_x_ bilirubin
_x_ protein	_x_ urobilinogen
_x_ ketone	_x_ sediment
_x_ blood	
_x_ nitrite	

Urine constituents were measured semi-quantitatively using test strips (Combur-9-test RL, Boehringer, FRG) and a reflection photometer (Urotron RL9 model). Sediment was evaluated microscopically, while specific gravity was determined using a urine refractometer.

Only a slight increase in urobilinogen and bilirubin were observed in male dogs on study days 184 and 368. No other apparent effects of treatment on urine parameters were reported.

9) **Anatomic and Histologic Pathology:**

The weight of the brain, thyroid with parathyroid, liver, kidneys, pituitary, adrenals, testes, and ovaries were weighed in all animals. The following tissues were examined macroscopically, and then preserved for histopathological examination:

Digestive	Respiratory	Urogenital
_x_ tongue	_x_ trachea	_x_ kidneys*
_x_ salivary glands*	_x_ lungs*	_x_ urinary bladder*
_x_ esophagus*	_-_ nasal cavity	_x_ testes*
_x_ stomach*	_x_ tonsils	_x_ epididymides*
_x_ duodenum*		_-_ seminal vesicle*
_x_ jejunum*	_x_ aorta*	_x_ prostate

(cont.)

x ileum*	x heart*	x ovaries
x cecum*	x bone marrow*	x uterus*
x colon*	x lymph nodes*	x vagina
x rectum*	x spleen*	
x liver*	x thymus*	
x pancreas*		

Neurologic	Glandular	Other
x brain*	x adrenals*	x bone
x peripheral nerve*	- lacrimal gland	x skeletal muscle
x spinal cord (3 levels)*	x mammary gland	x skin*
x pituitary*	x parathyroids*	x all gross lesions*
x eyes	x thyroids*	

*EPA guideline requirement "-" not examined

a) Anatomic Pathology:

i) Organ Weights

Statistical analysis of absolute and relative organ weights showed a significant increase in relative liver weight in male dogs from the 150ppm dose group (2.871kg in controls vs 3.287 kg at 150ppm, an increase of 14% [$p < 0.05$]). Relative liver weight was also increased in female dogs from the 50ppm dose level, from 3.072kg in controls to 3.814 at 50ppm, an increase of 24% ($p < 0.05$]). Relative liver weight in females from the 150ppm dose group was comparable to control dogs. There were no other apparent changes in absolute or relative organ weights in this study.

ii) Macroscopic Lesions

Lesions in the liver of one male dog and two female dogs from the 150ppm dose group were observed. In the case of the male dog (#141:6), a granular surface of the whole liver with focal concretions on the capsular surface and in the gallbladder were reported (page 725 of the report). Size of the testes and prostate were reduced in this same dog, in addition to slight icterus, serous abdominal effusion, and body weight loss. In another dog from the 150ppm dose group (#161:6), thickening of the gallbladder wall was noted macroscopically, but could not be confirmed at the microscopic level. Dog # 201:6 showed erosions of the gastric mucosa.

In female dogs # 178:6 and 206:6, diffuse parenchymal discoloration (slight or light yellow) was observed upon examination of the liver. Concretions in the gallbladder were also observed in female dog 206:6 in addition to the liver lesions. The other lesions reported were considered incidental and not related to administration of test article.

Microscopic Lesions

eposition of iron positive pigment in Kupffer cells and/or hepatocytes was observed in the liver c control and treated dogs to varying degrees. A summary of the severity of this lesion is made low:

TABLE 4
Liver Pigmentation in Male and Female Dogs from
52 week Oral Administration of Dazomet[a]

	Dose Groups							
	males (ppm)				females (ppm)			
	0	15	50	150	0	15	50	150
dogs amined	6	6	6	6	6	6	6	6
positive pigment								
inimal	5	4	4	1	4	3	0	0
ight	1	2	2	4	2	3	5	2
derate	0	0	0	1	0	0	1	2
rked	0	0	0	0	0	0	0	2

ata taken from page 726 of report.

As shown, an increase in severity of pigmentation was observed for male dogs in the 150ppm se group, while an increase was observed for female dogs in the 50 and 150ppm dose group. e average degree of severity was higher in females than in males. The two female dogs obser h marked pigmentation in the liver were also observed to have severe chronic active hepatitis. Other microscopic lesions considered treatment related included minimal erosions of the fundic ucosa in 3 male dogs from the 150ppm dose level, an increase from 1 control dog to 6 dogs at t 0ppm dose level with minimal round cell infiltration in the submucosa of the esophagus, slight ultifocal testicular atrophy in 2 dogs from the 150ppm dose group, marked alveolar atrophy of th ostate in 1 dog from the 150ppm dose group, and a moderate decrease in bone marrow cellula m one female in the 50ppm dose group.

III. DISCUSSION

In the present study, the chronic oral toxicity of dazomet was evaluated in male and female beagle dogs by administration of test compound in the diet for 12 months. Observations for mortality were made twice a day, and observations for clinical toxicity were made once daily. Body weight was recorded weekly, and food consumption was measured daily. Clinical pathology (hematology and clinical chemistry) measurements were made prior to study initiation, and again on study days 95, 186, and 366 or 368. Urinalysis was conducted 5 days prior to study initiation and again at 92 or 93, 184, and 366 or 368 days after study initiation. Ophthalmoscopic examination was performed prior to the start of the study and again at study termination. Anatomic and histopathologic examination were performed at study termination on all animals. Selected organs (parathyroid, liver, kidneys, pituitary, adrenals, testes, and ovaries) were weighed from all dose groups of dogs including controls.

No mortality was reported in this study, and clinical signs of toxicity were limited to emaciation in one female dog from the 150ppm dose group which occurred from day 267 to the end of the study. No changes in group mean absolute body weight were observed in this study. Group mean body weight gain was affected in one male dog from the 150ppm dose level, and was unaffected in treated female dogs. In male dogs, body weight gain was affected for the study duration (days 0-364), in which body weight gain of the 150ppm dose group was 61% of control. This was due to weight loss in one dog of this group (141:6). No decrease in body weight gain was observed at lower doses of test article in male dogs.

Measurement of food consumption for male and female dogs showed no significant decrease in food consumption for male dogs. In female dogs, food consumption was decreased in 3 of the 6 dogs (#'s 150:6, 200:6, and 206:6) for the first 20 days of test article administration by 50-100 grams. Food efficiency was not significantly affected for the first 90 days in either male or female dogs. However, for the study duration (days 0-363), food efficiency was decreased from 1.0 in control male dogs to 0.7 at the 150ppm dose level. In female dogs, food efficiency for the study period 0-363 days was decreased from 1.0 in the control group to 0.6 in the 15 and 150ppm dose groups. Interpretation of these findings is made difficult by the apparent decomposition of test article at room temperature during the one hour feeding period (page 44 of the report, section 4.1.2. It is possible that the decreased food efficiency observed is test article related or related to palatability as a result of test article breakdown, as some dogs were fed outside (page 24 of the report). Considering that dereases in food efficiency were observed after the first 90 days, and that the period after the first 90 days covered the summer months (June, July, August), an alteration in palatability as a result of test article breakdown is a possibility.

Alterations in hematology were limited to a decrease in red blood cells, hemoglobin, and hematocrit in one male dog (141:6) from the 150ppm dose group on day 366 compared to control values. This same dog also displayed significant increases in serum alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase on study days 95, 186, and 366, and

ɔased bilirubin, globulins, and decreased albumin on day 366. In female dogs, treatment relatec
:ts on enzyme activites were apparent in two dogs from the 150ppm dose group (#'s 178:6 and
6). A progressive increase in values for alanine aminotransferase, aspartate aminotransferase,
alkaline phosphatase were observed over the course of the study, such that by the end of
.ment, group mean alanine aminotransferase was elevated almost 300%, aspartate
ıotransferase 45%, and alkaline phosphatase 101% in comparison to controls. Decreased
m albumin was also observed at the 150ppm dose level. The effects in female dogs can be
ɔidered treatment related.
'gan weight changes were limited to the liver in both sexes. In male dogs, a significant increase
er : body weight ratio was observed at the 150ppm dose level, while a similar observation was
d in female dogs at the 50ppm dose level. According to the pathology report supplied by the
ɔtrant (page 729), histopathologic liver changes were not sufficient to explain these increases.
ever, the chronic active hepatitis found in high dose female dogs (178:6, 206:6), and the
ɔsis observed in one high dose male dog (141:6) could be considered to contribute to this
ɔase in relative liver weight.
:oss pathological findings consisted of a granular surface of the liver with concretions in one
ɔ dog from the 150ppm dose group (141:6), and diffuse discoloration of the liver parenchyma in
ɔale dogs of the 150ppm dose group (178:6, 206:6). Microscopically, the liver of treated dogs
ved an increase in severity of iron-positive pigment, which was apparently dose-related.
ɔased pigment deposition in Kupffer cells was considered as an indication of a multistep
ogenesis of liver cell injury (page 728 of the report), supporting the liver as a target organ of
ɔmet toxicity.
:her microscopic lesions considered treatment related included minimal erosions of the fundic
osa in 3 male dogs from the 150ppm dose level, an increase from 1 control dog to 6 dogs at the
ɔpm dose level with minimal round cell infiltration in the submucosa of the esophagus, slight or
ifocal testicular atrophy in 2 dogs from the 150ppm dose group, marked alveolar atrophy of the
tate in 1 dog from the 150ppm dose group, and a moderate decrease in bone marrow cellularity
one female in the 50ppm dose group. The significance of round cell infiltration and decreased
ɔ marrow cellularity was not established in this study.

ONCLUSIONS

ɔmet was administered to male and female beagle dogs at dose levels of 0, 15ppm (0.28
‹g/day, males; 0.35 mg/kg/day, females), 50ppm (1.05 mg/kg/day, males; 1.12 mg/kg/day,
ɑles), and 150ppm (3.15 mg/kg/day, males; 3.50 mg/kg/day, females). Toxicity in female dogs
evident at 50 and 150ppm dazomet, and included increased liver : body weight ratio, increasec
.m alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase activities,
'eased serum albumin, discoloration of the liver parenchyma, increased severity of iron positive
ıent deposition in the liver, and chronic active hepatitis. Toxicity in male dogs was limited to one
at the 150ppm dose level, who showed decreased body weight gain and similar signs as those
:tioned above for female dogs.

:emic NOEL = 15 ppm (females); = 50 ppm (males)
:emic LEL = 50 ppm (females; increased liver : body weight ratio)
= 150 ppm (males; decreased body weight gain; hematological effects)

80

V. CLASSIFICATION Core minimum

This study satisfies the guideline requirements (83-1) for a chronic oral toxicity study in dogs.

BASF
Abteilung Toxikologie
Department of Toxicology

3.10. Statistical evaluation

The statistical evaluation of the data was carried out on the computer systems of the Department of Toxicology (responsible: Dr. Hoffmann, ZST).

3.10.1. Clinical examinations

Means and standard deviations were calculated for the variables (feed consumption, body weight, body weight change and intake of the test substance) for the statistical evaluation.

The statistical significances for body weight and body weight change were calculated using a KRUSKAL & WALLIS TEST (1) or a MANN-WHITNEY U TEST (2) for the comparison of several dose groups with a control group.

Significances resulting from this test have been indicated in the tables (* for $p < 0.05$, ** for $p < 0.02$ and *** for $p < 0.002$).

1) The KRUSKAL-WALLIS one way analysis of variance by ranks.
In: SIEGEL, S. (1956): Nonparametric Statistics for the behavioral sciences, pp. 184 - 194, McGraw-Hill Book Company, New York, Toronto, London.

2) The MANN-WHITNEY-U-Test.
In: SIEGEL, S. (1956): Nonparametric Statistics for the behavioral sciences, pp. 116-127, McGraw-Hill Book Company, New York, Toronto, London

Reviewed by: Timothy F. McMahon, Ph.D.
Section I, Toxicology Branch II (H7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. 10/16/91
Section I, Toxicology Branch II (H7509C)

Data Evaluation Report

Study type: Carcinogenicity - rats
Guideline: 83-2a

EPA ID Numbers: MRID number: 418650-01
Caswell No: 840
HED Project No: 1-1669

Test material: Dazomet

Synonyms: tetrahydro-3,5-dimethyl-2 H-1,3,5-thiadiazine-2-thione

Study number(s): 70C0318/8584

Sponsor: BASF Corporation
Agricultural Chemicals Group
Research Triangle Park, NC

Testing Facility: BASF Aktiengesellschaft
Department of Toxicology
W. Germany

Title of report: Report on the Oncogenic Potential of Dazomet In Rats After 24 Month Administration in the Diet

Author(s): Dr. B. Kuhbroth

Study Completed: July, 1989

Conclusions:

Technical Dazomet was administered to male and female rats in the diet for 104 weeks doses of 0ppm, 5ppm (0.2 mg/kg/day males; 0.3 mg/kg/day females), 20ppm (0.9 mg/kg/d males; 0.84 mg/kg/day females), and 80 ppm (3.71 mg/kg/day males; 4.83 mg/kg/day females). There was no apparent systemic toxicity in either sex at any dose level used in t study. In male and female rats, there was a non-statistically significant increase in malign lymphoma at 80ppm test article, while in female rats, there was a non-statistically significa increase in mammary fibroadenoma and adenocarcinoma at 80ppm. Non-neoplastic lesi

in the form of hepatocellular fat deposition and vacuolation (male rats) and mixed cell and basophilic cell foci (female rats) were increased at the 80ppm dose level.

There is no evidence contained in this study which supports the conclusion that the Maximum Tolerated Dose (MTD) was achieved. In a subchronic toxicity study in rats (MRID 418655-02), the MTD appeared to have been reached at 360ppm, the highest dose used this study. However, the highest dose in the present study (80ppm) does not approximate highest dose used in the subchronic study. Thus, the high dose tested in this study was not considered to be adequate to assess the carcinogenic potential of dazomet.

The Systemic Toxicity No Observed Effect Level (NOEL) = 20 ppm

The Systemic Toxicity Lowest Observed Effect Level (LEL) = 80 ppm (increased incidence neoplastic and non-neoplastic pathology, males and females)

The Maximum Tolerated Dose (MTD)- not achieved

V. CLASSIFICATION

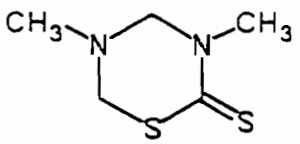
Core Supplementary

This study does not satisfy the guideline requirements (83-2) for a carcinogenicity study in rats. Based upon the lack of an MTD and evidence of carcinogenicity, this study cannot be upgraded.

I. MATERIALS AND METHODS

A. Test Material Dazomet

purity:98.2%; batch # 26-5297
description: not given in this study; described as a "white powder with a tinge of gray " in MRID# 418655-01.
structure:



B. Vehicle: dietary preparation

C. Test Animals: Species: Wistar rat (Chbb=THOM [SPF]), male and female
Source: Dr. Karl Thomae, Biberach an der Riss, FRG.
Age: 42 days old at study initiation.
Weight (mean): males, 178g (range:160-200g); females, 146g (rang 128-166g).

D. Dietary Preparation and Analysis

Dazomet was incorporated into ground diet at the required concentrations by weighing t required amount of test substance and mixing with a small amount of food in a beaker usi a spatula. This premix was subsequently prepared in a BOSCH household mixer. Additio amounts of food were then added to the premix to obtain the desired final concentration, a mixing was carried out in a GEBR.LODIGE laboratory mixer for 10 minutes. Test diets were prepared twice a week and stored at 4 °C as soon as possible after mixing.

Stability and purity of test substance at room temperature for the duration of the study wa stated to have been performed prior to the start of the present study (page 24 of the report) Stability of test material in ground feed at room temperature was shown to be 1 day as reported on page 1302 of the report. The registrant stated, however (page 24 of the report that the stability of test material in ground feed was 2 days at room temperature, and provi data in support of this (page 1301 of the report). Stability of test material in ground feed at °C was 4 days (page 1302 of the report). During the conduct of the study, samples of feed were analyzed for test material concentration approximately every month. Food given to th

rats was changed daily during the first 2 study days, and every other day thereafter, as stability of test material for 2 days in feed could be verified.

Homogeneity of test material in feed was checked using samples from the lowest (5 and 20ppm dose levels) and highest dietary concentrations taken at the beginning of the study. Results (page 1298 of the report) showed that for a nominal dietary concentration of 5ppm, actual concentrations of test material ranged from 79-89% of nominal, and for a nominal dietary concentration of 20ppm, actual concentrations ranged from 95-106% of nominal. At nominal dietary concentration of 320ppm, actual concentrations ranged from 95-99% of nominal.

TABLE 1

Analysis of Test Diet Samples[a]

Study Week (approx.)	Dazomet found (ppm) 5ppm[b]	20ppm	80ppm
0	--	16.7	69.1
6	--	17.3	76.5
11	4.1	17.0	68.8
16	4.4	17.5	69.2
28	4.4	17.0	68.1
53	4.2	19.4	68.0
78	4.8	16.0	65.3
104	4.5	17.8	72.4

[a]data from pages 1303-1321 of report

[b]samples from the 5ppm dose group were not sent for analysis during the first five weeks of the study. No reason was stated for this omission.

Dietary concentrations of Dazomet ranged from 4.1-4.8 ppm in the 5 ppm dose group, from 16.0-19.4 ppm in the 20 ppm dose group, and from 65.3-76.5 ppm in the 80 ppm dose gro In large part, dietary concentrations of test article at all dose levels were not within 10% of nominal concentrations. For the sampling times listed above, the average dietary concentration at 5ppm was 12% below nominal, 14% below nominal at 20ppm, and 13% below nominal at 80ppm. Thus, the average dose level at each dose would be 4.4ppm , 17.2ppm , and 69.6ppm corresponding to doses of 0.2 mg/kg/day, 0.86 mg/kg/day, and 3.5 mg/kg/day.

D. Animal Husbandry

Two hundred male and 200 female rats were used in this study. Rats were free from any signs of disease upon receipt. Rats were acclimated to the laboratory environment for 8 da prior to test article administration.

Rats were housed singly during test article administration in type DK III stainless steel wir mesh cages (Becker and Co., FRG). Rats were assigned to the various test groups 1 day p to study initiation according to random allocation based upon body weight. All rats had fre access to food (Kliba 343 rat/mouse/hamster maintenance diet) and drinking water during acclimation and test article administration. Rats were housed in temperature (20-24 °C) an humidity (30-70%) controlled rooms.

One day prior to study initiation, each rat was randomly assigned by computerized random number generation to the various treatment groups as outlined below:

Group #	Dose Level (ppm)	No. of rats (animal #'s) male	female
0	0	50 (201-250)	50 (401-450)
1	5	50 (251-300)	50 (451-500)
2	20	50 (301-350)	50 (501-550)
3	80	50 (351-400)	50 (551-600)

E. Statistical Analysis

From page 30 of the registrant's report: "The statistical evaluation and calculation of the data was carried out on the computer systems of the Department of Toxicology (Dr. H.D. Hoffmann, responsible).

F. Compliance

A signed data confidentiality claim statement was provided.

A signed statement of GLP compliance provided. This study was conducted according tc OECD guidelines.

A signed statement of quality assurance was provided.

II. OBSERVATIONS AND RESULTS

A. Mortality

All rats were observed for moribundity and mortality twice daily during weekdays, and once daily on weekends during the course of the study.

Cumulative mortality in male and female rats is summarized in the following Table:

TABLE 2
Cumulative Mortality in rats Given Dazomet in the Diet for 104 Weeks [a]

Week of Study	Males 0	Males 10	Males 500	Males 2000	Females 0	Females 10	Females 500	Females 2000
1	0(0)[b]	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
13	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
24	1(2)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
52	1(2)	1(2)	2(4)	1(1)	1(2)	0(0)	0(0)	1(2)
78	3(6)	1(2)	4(8)	2(4)	3(6)	3(6)	4(8)	2(4)
91	9(18)	3(6)	10(20)	7(14)	10(20)	10(20)	10(20)	6(12)
104	14(28)	6(12)	20(40)	17(34)	20(40)	20(40)	21(42)	14(28)

[a] data taken from pages 102-103 of registrant report.

[b] cumulative mortality (percent mortality). Data for week 1 of the study not specifically provided, but survival assumed to be 100%.

No apparent changes in mortality related to administration of test material were observed either male or female rats over the course of this study.

B. Body Weights

Body weights of all rats were determined once a week for the first 3 months of the study, ar at monthly intervals thereafter. Body weight change was recorded as the difference betwee body weight on the day of weighing and body weight on day 0 of the study.

Examination of data presented as group mean body weights and body weight change (Tables 011-030, pages 61-80 of the report) showed no significant effects of test article administration on group mean absolute body weight in male or female rats. In addition, no effect of test article was observed on body weight gain in male rats either at 91 days or for t duration of the study. A significant ($p < 0.05$) decrease in group mean body weight gain wa recorded for female rats at 91 days in the 80ppm and 5ppm dose groups. However, there was no dose-related trend, and group mean body weight gain for female rats at study termination was equivalent between dose groups. These effects are summarized in the following Table:

TABLE 3
Group Mean Body Weight Gain in Male and Female Rats from 104 Week Dietary Administration of Dazomet[a]

	Dose Groups							
	males (ppm)				females (ppm)			
Body Weight (g)	0	5	20	80	0	5	20	80
week 0	176.8 ±7.4	179.1 ±8.3	179.2 ±8.7	178.2 ±8.6	144.0 ±6.7	146.1 ±7.4	146.3 ±7.3	145.6 ±7.1
Weight gain:								
days 0-91	293.5 ±29.7	275.5 ±35.6	286.0 ±34.0	283.5 ±34.7	131.7 ±18.3	122.2* ±18.2	123.7 ±16.5	122.0* ±17.9
days 0-728	581.9 ±126.6	628.0 ±108.8	591.6 ±118.7	616.2 ±112.0	288.7 ±66.7	298.3 ±88.8	285.4 ±56.5	292.7 ±98.5

[a] data taken from Tables 011-030, pages 61-81 of the report.

[b] $p < 0.05$ vs control.

C. Food Consumption and Efficiency

Food consumption was calculated for each rat once a week for the first 3 months of the study, and at monthly intervals thereafter. Food efficiency was calculated using the following formula:

$$\frac{BW_x - BX_{x-y}}{FA \times y} \times 100$$

BW_{x-y} = mean body weight at weighing prior to day x

BW_x = body weight on day x

FA = food consumption from day x-y to day x

y = interval in days between weighings

Group mean food consumption (Tables 001-010, pages 51-60) and food efficiency (Tables 031-040, pages 81-89) were not affected by administration of test article to either male or female rats in a manner which would suggest test article toxicity.

D. Intake of Dazomet

Intake of test article (mg/kg) was calculated at the same time at which food consumption was determined, using the following formula:

$$\frac{FA \times D}{BW_x}$$

FA = mean food consumption from day x-y to day x

D = dose in ppm

BW_x = body weight on day x

The group mean intake of Dazomet for male and female rats over the course of the study is summarized in the following table (Table 4):

TABLE 4

Group Mean Dietary Intake of Dazomet in Male and Female Rats Over 104 Weeks [a]

Dose Group (ppm)	Nominal mg/kg/day (ppm/20)	Average Intake (weeks 0-104 (mg/kg/day) males	females
0	0	0	0
5	0.25	0.25 (0.22)	0.34 (0.30)
20	1.0	1.04 (0.90)	0.97 (0.84)
80	4.0	4.26 (3.71)	5.55 (4.83)

[a]data taken from Tables 041-050, pages 90-99 of registrant report.

Group mean intake of Dazomet across all dose groups was calculated based upon nomi levels of test article in feed. However, as noted above (Table 1, page 4 of DER) actual lev of test article in feed ranged from between 12-14% below nominal levels. Thus, actual do received by rats in the various dose groups are as shown above in parentheses for a intake of test material. When this is taken into account, test article intake ranged from 84-120% of nominal across all dose groups.

E. Clinical Signs and Pathology

Rats were individually monitored for signs of toxicity and pharmacologic effects once e day. Inspection and palpation were performed once a week in addition.

A summary of clinical observations for male and female rats (Tables 051-052, pages 10 101) was provided. There were no apparent observations which could be considered tes article related, with the exception of an apparent dose-related increase in the number of female rats with palpable (ulcerated) masses. This finding increased from 0 rats in contro 2 rats in the 5ppm dose group, 3 rats in the 20ppm dose group, and 5 rats in the 80ppm group.

F. Hematology

Blood was obtained for hematologic analysis following decapitation. Blood smears for differential blood counts were obtained from surviving rats of the control and 80ppm dose groups. Smears were also obtained from all rats killed *in extremis* during the study. Sme were stained with Wright's stain and evaluated microscopically.

Note: According to OECD guidelines, "at 12 months, 18 months, and prior to sacrifice, a blood smear is obtained for all animals. A differential blood count is performed on sample

those animals in the highest dosage group and the controls." No blood samples appear t have been taken at 12 or 18 months in the present study.

Administration of dazomet had no apparent effect on the results of differential blood coun analysis in either male or female rats, with the exception of a change in the appearance o the nucleus and plasma of lymphocytes from male rats in the 80ppm dose group, and an increase in juvenile lymphocytes from female rats in the 80ppm dose group. The registra did not consider these changes to be substance related, as the degree of change was nc severe, and no changes of this nature were observed in the chronic toxicity study (# 70C0318/8583). The increase in atypical lymphocytes found in the blood of male and female rats at this dose was considered the result of aging.

G. Organ Weights

The weight of the liver, kidneys, adrenal glands, brain, and testes was determined in a rats killed on schedule. As summarized by the registrant (page 412 and 433-437 of the report), there were no significant test article-related changes in absolute organ weights o organ:body weight ratios in either male or female rats.

H. Macroscopic Observations

All rats surviving to the end of the study as well as those dying or killed during the study were killed by decapitation under carbon dioxide anesthesia. All organs were examined and all macroscopic findings recorded at necropsy.

Summaries of macroscopic findings are presented in tabular form on pages 439-464. Examination of these data shows that enlargement of the spleen and iliac lymph nodes v observed in male rats from the 20 and 80ppm dose groups upon gross examination. Of a rats examined in these two dose groups, 5 of 50 rats were observed with enlarged splee the 20ppm dose group, while 6 of 50 rats in the 80ppm dose group were observed with t pathology. No enlargement of the spleen was observed at doses below 20ppm, suggest test article related effect. Enlargement of the iliac lymph nodes was observed in a total o rats from the 20ppm dose group, and 7 rats from the 80ppm dose group. Enlargement of iliac lymph nodes was observed in one rat each from the 0ppm and 5ppm dose groups, suggesting again a test article effect. No other significant gross pathology was observed either male or female rats.

H. Microscopic Observations

The following tissues were removed and preserved in 4% formaldehyde solution (page 408) :

Digestive	Respiratory	Urogenital
- tongue	x trachea*	x kidneys*
x salivary glands*	x lungs*	x urinary bladder*
x esophagus*	- nasal cavity	x testes*
x stomach*		x epididymides*
x duodenum*	Cardiovascular	x seminal vesicle*
x jejunum*	x aorta*	x prostate
x ileum*	x heart*	x ovaries*
x cecum*	x bone marrow*	x uterus*
x colon*	x lymph nodes*	- vagina
- rectum*	x spleen*	
x liver*	x thymus*	
x pancreas*		
x gall bladder*		

Neurologic	Glandular	Other
x brain*	x adrenals*	x bone (femur)*
x peripheral nerve*	- lacrimal gland	x skeletal muscle*
x spinal cord (3 levels)*	x mammary gland*	x skin*
x pituitary*	x parathyroids*	x all gross lesions*
x eyes*	x thyroids*	

*OECD guideline requirement "-" not examined

Tissues listed above were trimmed, processed, and embedded in paraffin wax. Hematoxylin and eosin stain was applied to sections of all tissues from rats in control and high dose groups, and to tissues from rats in the low and mid dose groups that died or were killed in extremis. The remainder of rats in the low and mid dose groups received microscopic examination of only the lungs, liver, spleen, kidneys, and all gross lesions.

In addition to H & E stain, frozen sections of the liver of all rats were stained with oil red O for detection of fat, and the spleen stained additionally with Prussian blue for detection of iron.

1) Neoplastic Observations

Data on neoplastic lesions were provided in several formats by the registrant. In one format, data from all rats were presented (pages 488-492); in others, data were divided in

lesions observed only in those rats surviving to study termination (pages 497-500) and lesions observed in those rats killed during the study (pages 493-496). A general evaluati of rats with neoplasms was provided (pages 506-511) as well as a listing of neoplasms an metastases according to animal number (pages 512-532). Review of these data indicated that in large part, there did not appear to be any significant effects of test article administra on neoplastic development in male or female rats. However, a few types of neoplastic lesi were apparently increased in rats at the 80ppm dose level which need to be addressed by the registrant. These are summarized below (Table 5):

TABLE 5

Neoplastic Lesions in Male and Female Rats Given Dietary Dazomet for 104 Weeks[a]

	Males				Females			
Dose (ppm)	0	5	20	80	0	5	20	80
Number of animals	50	50	50	50	50	50	50	50
malignant lymphoma	7[b](14)[c]	4(8)	7(14)	10(20)	3(6)	10(20)	4(8)	6(12)
mammary gland								
fibroadenoma					9(18)	11(22)	12(24)	14(28)
adenocarcinoma					3(6)	6(12)	5(10)	8(16)

[a]data taken from page 489 of the report.

[b]number of rats with lesion; [c]percentage of rats with lesion

a) **malignant lymphoma**, observed in 7/50 male and 3/50 female control rats and in 10/ male and 6/50 female rats from the 80ppm dose group. The incidence of this neoplastic lesion was increased in both sexes at the 80ppm dose level, with the incidence doubled ir female rats.

b) **mammary gland fibroadenoma and adenocarcinoma** in female rats. Mammary gland fibroadenoma increased from 9/50 control female rats to 14/50 female rats at the 80ppm dose level. Mammary gland adenocarcinoma increased from 3/50 control female r to 8/50 female rats at the 80ppm dose level.

These lesions were not addressed by the registrant. They may represent variation within t strain of rat from this laboratory (which will need to be verified by the registrant) or they ma represent a treatment related effect. It appears from the report that there is no statistical difference between control and high dose rats. Historical control data for these lesions are requested in order to determine the significance of the above neoplastic lesions in this stu

2) Non-Neoplastic Observations

Data provided by the registrant on non-neoplastic lesions (beginning on page 467) in th study were given in a similar format as that for neoplastic lesions (see above, neoplastic observations).

The registrant stated (page 413 of the report) that non-neoplastic lesions between contr and treated rats were not remarkable, with the following exceptions summarized below:

TABLE 6

Non-Neoplastic Lesions in Male and Female Rats Given Dietary Dazomet for 104 Week

	Males				Females			
Dose (ppm)	0	5	20	80	0	5	20	8
Number of animals	50	50	50	50	50	50	50	5
Liver								
fat deposition, diffuse	3[b](6)[c]	2(4)	1(2)	8(16)	1(2)	0(0)	1(2)	2(
vacuolation	7 (14)	12(24)	11(22)	18(36)	11(22)	6(12)	11(22)	10
mixed cell foci	7(14)	14(28)	13(26)	8(16)	4(8)	4(8)	1(2)	8
basophilic cell foci	3(6)	1(2)	2(4)	4(8)	3(6)	2 (4)	2(4)	9

a- data taken from pages 469-470 of the report. b-number of rats with lesion
c- percentage of rats with lesion.

a) **diffuse hepatocellular fat deposition**: observed in 3/50 male control rats and 8/50 male high dose rats (incidence in low and mid dose rats was 2/50 and 1/50, respectively).

b) **hepatocellular vacuolation**: observed in male rats with the following incidence- (7/50 controls; 12/50 low dose; 11/50 mid dose; 18/50 high dose).

c) **mixed cell foci**: observed in female rats with the following incidence (4/50 controls; 4/50 low dose; 1/50 mid dose; 8/50 high dose)

d) **basophilic cell foci**: observed in female rats with the following incidence (3/50 controls; 2/50 low dose; 2/50 mid dose; 9/50 high dose). The combined incidence of altered cell foci was also increased in high dose female rats vs control female rats (17/50 vs 8/50 rats for this lesion).

III. DISCUSSION

In the present study, male and female rats were administered Dazomet in the diet for 104 weeks at levels of 0ppm, 5ppm (0.2 mg/kg/day), 20ppm (0.86 mg/kg/day), and 80 ppm (3.6 mg/kg/day) as a means of determining the carcinogenic potential of this compound. Rats were monitored for treatment related effects on mortality, body weight gain, food consumption, palpable masses, and clinical signs of toxicity. At study termination, rats were killed and tissues were harvested and preserved for examination of both potential neoplastic and non-neoplastic changes related to treatment with Dazomet.

There was a notable lack of effects from test article administration in this study. No effects were noted in mortality, body weight , body weight gain, food consumption and efficiency, clinical pathology and hematology, and absolute and relative organ weight in either male or female rats at any dose level. However, splenic enlargement as well as enlargement of the iliac lymph nodes was observed in male rats at the 20ppm and 80ppm dose levels, which appeared test article related. No corresponding effect was noted in female rats at these dose levels.

The effects of test article administration on tumor formation in male and female rats was manifested primarily by an apparent increase in the number of male and female rats at the 80ppm dose level with malignant lymphoma, and an increase in the number of female rats with mammary gland fibroadenoma and adenocarcinoma at the 80ppm dose level. However, these differences were not statistically significant. Thus, the observed changes may represent variation in these tumor types within this strain of rat from this laboratory. The registrant is asked to supply historical control data in support of this.

Non-neoplastic lesions were also found to be increased in treated male and female rats. Specifically, diffuse hepatocellular fat deposition and hepatocellular vacuolation were observed in increased incidence in male rats in the 80ppm dose group in comparison to control (8/50 vs 3/50 for fat deposition, and 18/50 vs 7/50 for vacuolation). In female rats, mixed cell foci and basophilic cell foci were found in increased incidence in rats from the

80ppm dose group in comparison to control (8/50 vs 4/50 for mixed cell foci; 9/50 vs 3/50 for basophilic cell foci). These effects were considered test article related by the registrant. However, significant effects of test article on non-neoplastic pathology were not observed at lower doses of test article.

The following study deficiencies were observed and are noted:

1) Hematological analysis was not performed at 12 and 18 months during the study, as required in OECD guidelines.

2) No historical control data are provided to support the conclusions of the tumor findings in this study.

IV. CONCLUSIONS

Technical Dazomet was administered to male and female rats in the diet for 104 weeks at doses of 0ppm, 5ppm (0.2 mg/kg/day males; 0.3 mg/kg/day females), 20ppm (0.9 mg/kg/day males; 0.84 mg/kg/day females), and 80 ppm (3.71 mg/kg/day males; 4.83 mg/kg/day females). There was no apparent systemic toxicity in either sex at any dose level used in this study. In male and female rats, there was a non-statistically significant increase in malignant lymphoma at 80ppm test article, while in female rats, there was a non-statistically significant increase in mammary fibroadenoma and adenocarcinoma at 80ppm. Non-neoplastic lesions in the form of hepatocellular fat deposition and vacuolation (male rats) and mixed cell and basophilic cell foci (female rats) were increased at the 80ppm dose level.

There is no evidence contained in this study which supports the conclusion that the Maximum Tolerated Dose (MTD) was achieved. In a subchronic toxicity study in rats (MRID # 418655-02), the MTD appeared to have been reached at 360ppm, the highest dose used in this study. However, the highest dose in the present study (80ppm) does not approximate the highest dose used in the subchronic study. Thus, the high dose tested in this study was not considered to be adequate to assess the carcinogenic potential of dazomet.

The Systemic Toxicity No Observed Effect Level (NOEL) = 20 ppm

The Systemic Toxicity Lowest Observed Effect Level (LEL) = 80 ppm (increased incidence of neoplastic and non-neoplastic pathology, males and females)

The Maximum Tolerated Dose (MTD)- not achieved

V. CLASSIFICATION
Core Supplementary

This study does not satisfy the guideline requirements (83-2) for a carcinogenicity study in rats. Based upon the lack of an MTD and evidence of carcinogenicity, this study cannot be upgraded.

Reviewed by: Timothy F. McMahon, Ph.D. 10/11/91
Section I, Toxicology Branch II (H7509C)
Secondary Reviewer: Yiannakis M. Ioannou, Ph.D. 10/15/91
Section I, Toxicology Branch II (H7509C)

Data Evaluation Report

Study type: Carcinogenicity - mice
Guideline: 83-2

EPA ID Numbers: MRID number: 418651-01
Caswell No: 840
HED Project No: 1-1900

Test material: Dazomet technical

Study number(s): 65C0318/8585

Sponsor: BASF Corporation
Agricultural Chemicals Group
Research Triangle Park, N.C.

Testing Facility: BASF Aktiengesellschaft
Department of Toxicology
West Germany

Title of report: Report on the Study of the Oral Toxicity of Dazomet in Mice After 78 Week Administration in the Diet

Author(s): Dr. B. Kunbroth

Study Completed: August 18, 1982

Conclusions:
Technical dazomet was administered to male and female B6C3F1 mice in the diet for 78 weeks at doses of 0ppm, 20ppm (3.9 mg/kg/day in males, 5.7 mg/kg/day in females), 80ppm (15.6 mg/kg/day in males, 21.4 mg/kg/day in females), and 320ppm (69.9 mg/kg/day in males, 95.0 mg/kg/day in females). Decreased body weight, body weight gain, and food efficiency were observed in male mice from the 320ppm dose group. Increased liver weight and liver : body weight ratio was observed in male and female mice from the 320ppm dose group sacrificed at 52 and 78 weeks. Incidence of hepatocellular adenoma was increased in male and female mice from the 320ppm dose group, and in male mice from the 80ppm dose group. A statistically significant trend for increased hepatocellular adenoma and basophilic foci of cellular alteration in the liver was reported in female mice.

Based on the effect of test article on body weight gain in male mice, liver weight in male and female mice, and incidence of basophilic foci of cellular alteration in male and female mice during weeks 0-78 of the study, it appears that the MTD was achieved for dazomet.

The data in this study support the conclusion of limited evidence of carcinogenicity for technical Dazomet, based upon the occurrence of increased incidence of hepatocellular adenomas in male and female mice at 320ppm dazomet.

The Systemic No Observed Effect Level (NOEL) = 20 ppm

The Lowest Observed Effect Level (LEL) = 80 ppm (increased liver masses in male mice at 78 weeks; increased liver weight in female mice at 78 weeks).

The Maximum Tolerated Dose (MTD) = 320 ppm (decreased body weight gain in male mice during weeks 0-13; increased liver weight and lipid deposition in male and female mice at 78 weeks; increased incidence of basophilic foci of cellular alteration in males and females at 78 weeks).

V. CLASSIFICATION

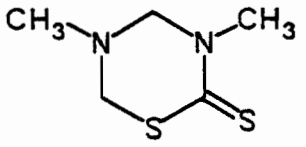
Core minimum

This study satisfies the guideline requirements (83-2) for a carcinogenicity study in mice.

I. MATERIALS AND METHODS

A. Test Material

Dazomet
purity:98.2%; batch # 26-5297
description: not given in this study; described as a "white powder with a tinge of gray " in MRID# 418655-01.
structure:



B. Vehicle: dietary preparation

Test article storage conditions were stated as "dry" (page 25 of the report).

C. Test Animals

Male and female B6C3F1 mice; Source: Charles River Wiga GmbH, West Germany. **Note** : This was stated as a deviation from the study protocol, as mice are normally obtained from Wilmington, Mass.

Weight (at study initiation): males, 20.9-25.4g; females, 17.2-20.2g.
Examination of individual mouse weights showed that mice were within the recommended weight range as specified in the guidelines.

D. Dietary Mixtures

Dazomet was incorporated into ground diet at the required concentrations by weighing the required amount of test substance and mixing with a small amount of food in a beaker using a spatula. This premix was subsequently prepared in a BOSCH household mixer. Additional amounts of food were then added to the premix to obtain the desired final concentration, and mixing was carried out in a GEBR.LODIGE laboratory mixer for 10 minutes. Test diets were prepared twice a week and stored at 4 °C as soon as possible after mixing.

Stability of test material in ground feed at room temperature was shown to be 1 day as reported on page 435 of the report. Test article was sufficiently stable in animal feed for 4 days when stored at 4 °C (page 435 of the report).

During the conduct of the study, samples of feed were analyzed for test material concentration approximately every six weeks by gas chromatography. Food given to the rats was replaced with freshly prepared diet every two days. Stability of test article in feed at room temperature for two days was demonstrated (page 434 of the report).

Homogeneity of test material in feed was checked using samples from study # 70C0318/8583, chronic toxicity of dazomet in rats, which was run concurrently with this study and used the same dietary concentrations. Samples of diet containing 5, 20, and 320 mg/kg dazomet were analyzed for homogeneity (pages 431-432 of the report). Results showed that for a nominal dietary concentration of 5ppm, actual concentrations of test material ranged from 79-89% of nominal, and for a nominal dietary concentration of 20ppm, actual concentrations ranged from 95-106% of nominal. At a nominal dietary concentration of 320ppm, actual concentrations ranged from 95-99% of nominal.

TABLE 1

Analysis of Test Diet Samples[a]

	Dazomet found (ppm)		
Study Week (approx.)	20ppm	80ppm	320ppm
0	20.1	74.1	299
6	17.3	76.5	289
11	17.0	68.8	292
16	17.5	69.2	303
28	17.0	68.1	290
53	19.4	68.0	307
78	16.0	65.3	299

[a]data from pages 436-450 of report

Dietary concentrations of dazomet ranged from 16.0-19.4 ppm in the 20 ppm dose group, 65.3-76.5 ppm in the 80 ppm dose group, and 290-307 ppm in the 320 ppm dose group. In large part, dietary concentrations of test article at the 20 and 80 ppm levels were not within 10% of nominal concentrations. For the sampling times listed above, the average dietary concentration at 20 ppm was 14% below nominal 13% below nominal at 80ppm, and 8% below nominal at 320 ppm. Thus, the average dose level at each dose would be 17.7ppm , 70.0ppm, and 297ppm .

E. Animal Husbandry

Two hundred forty male and 240 female mice were used in this study. Mice were free from any signs of disease upon receipt. Mice were acclimated to the laboratory environment for 8 days prior to test article administration.

Mice were housed singly during test article administration in type MI Makrolon cages (Becker and Co., FRG). Mice were assigned to the various test groups 1 day prior to study initiation according to random allocation based upon body weight. All mice had free access to food (Kliba 343 rat/mouse/hamster maintenance diet) and drinking water during acclimation and test article administration. Mice were housed in temperature (20-24 °C) and humidity (30-70%) controlled rooms.

One day prior to study initiation, each mouse was randomly assigned by computerized random number generation to the various treatment groups as outlined below:

Group #	Dose Level (ppm)	No. of mice (animal #'s) male	female
0	0	50 (1-50)	50 (241-290)
2	20	50 (61-110)	50 (301-350)
3	80	50 (121-170)	50 (361-410)
4	320	50 (181-230)	50 (421-470)

In addition to the above, groups of 10 mice/sex/dose were used as satellite animals for sacrifice at 52 weeks. Dose selection was based upon previous 91 day and 71 day feeding studies in mice conducted by the registrant in which doses of 20, 60, 180, 360, and 540ppm were used (91 day study) and doses of 1200 and 800ppm were used (71 day study). The major criterion for determining doses for the present study appears to have been the hematologic effects of dazomet in mice from these previous studies (page 23 of the report).

F. Statistical Analysis

According to the registrant (page 33), statistical evaluation and calculation of the data were carried out on the computer systems of the Department of Toxicology (Dr. H.D. Hoffmann, responsible).

G. Compliance

A signed statement of no data confidentiality claims was provided.

A signed statement of GLP compliance was provided. This study was conducted in accordance with OECD principles of good laboratory practice.

A signed statement of quality assurance was provided.

A signed statement of EPA flagging criteria was provided.

II. OBSERVATIONS AND RESULTS

A. Mortality and Clinical Observations

All mice were observed for moribundity and mortality at least twice daily during weekdays and once on weekends and holidays. Mice were examined daily for evident signs of toxicity and were palpated once a week. Clinical examinations were apparently not performed for weeks 36, 42, and 60 (individual animal tables; pages 314-409 of the report). It is stated on page 40 of the report that clinical examinations were performed once a week, in contrast to the statement made on page 31.

Cumulative mortality in male and female mice is summarized in the following Table:

TABLE 2
Cumulative Mortality in Mice Given Dazomet Technical in the Diet for 78 Weeks [a]

Week of Study	Males				Females			
	0	20	80	320	0	20	80	320
1	0(0)[b]	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
13	0(0)	1(2)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
26	0(0)	1(2)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
52	0(0)	1(2)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
78	0(0)	1(2)	2(4)	0(0)	1(2)	0(0)	0(0)	2(4)

[a] data taken from Tables 073-074, pages 121-122 of the report.

[b] cumulative mortality (percent mortality)

As is evident from these data, there were no effects of test article or dose of test article on survival in male or female mice in this study. Summary of the clinical observations in this study (pages 119-120). There were no apparent treatment-related findings in male or female mice.

B. Body Weights

Mice were weighed at the start of the study, weekly for the first 3 months of the study, and then monthly for the remainder of the study. Group mean body weights at selected times are presented in Table 3 .

TABLE 3
Group Mean Body Weights in Male and Female Mice Given Dazomet in the Diet for 78 Weeks[a]

Week of Study	Males (g) 0	20	80	320	Females (g) 0	20	80	320
0	23.3	23.2	23.2	23.4	18.6	18.5	18.7	18.8
13	31.5	29.7[c]	31.0	28.8[c]	25.2	25.5	26.3[c]	25.5
25	36.8	36.0	37.2	32.9[c]	28.0	29.4[b]	29.4[b]	28.4
53	40.1	39.7	41.7	38.0[c]	31.4	32.8	34.7[c]	32.8
78	42.9	40.8[b]	41.3	38.7[c]	34.5	34.5	36.7	33.4

[a]data taken from Tables 015-018 and 022-025, pages 63-66 and 70-73 of the report.
[b]$p < 0.05$ vs control; [c]$p < 0.01$ vs control

Statistically significant effects on group mean absolute body weights were observed in male mice in the 320ppm dose group almost consistently throughout the study from weeks 13-78, where absolute group mean body weight was decreased 9-11% vs concurrent control values. In female mice, the significant effects observed on absolute group mean body weight were increases in body weight among female mice of the 20 and 80ppm dose groups.

Changes in group mean body weight gain are summarized below for the 78 week study period (Table 4):

TABLE 4
Group Mean Body Weight Gain in Male and Female Mice Given Dazomet in the Diet for 78 Weeks[a]

	Males (g)				Females (g)			
	0	20	80	320	0	20	80	320
Body weight (week 0)	23.3	23.2	23.2	23.4	18.6	18.5	18.7	18.8
Weight gain (grams):								
0-13	8.1	6.6[c]	7.9	5.4[c]	6.6	7.0	7.5[c]	6.7
%control	-	81	97	66	-	106	113	101
0-53	16.8	16.5	18.5[b]	14.6[c]	12.8	14.3	15.9[c]	14.0
%control	-	98	110	86	-	111	124	109
0-78	19.5	17.7[b]	18.2	15.4[c]	15.9	16.0	18.0	14.6
% control	-	91	93	79	-	100	113	92

[a]data calculated from Tables 030-039, pages 81-87 of the report.

[b] $p < 0.05$ vs control; [c] $p < 0.01$ vs control.

As with group mean absolute body weights, significant effects in body weight gain were observed in male mice in the 320ppm dose group for the study duration. Body weight gain in this dose group was decreased to 66% of concurrent control for weeks 0-13 of the study, and to 78% of concurrent control for weeks 0-78. Other changes observed in group mean body weight gain were those of significant increases in weight gain, especially in female mice, which reflects the increased absolute body weight among treated female mice as shown in Table 3 above.

C. Food Consumption and Efficiency

Food consumption was determined for mice at the same times as body weight (once a week for the first 3 months and then monthly thereafter). Food efficiency was calculated as the ratio between body weight gain and the amount of feed simultaneously ingested according to the following formula (page 33 of the report):

$$\frac{BW_x - BX_{x-y}}{FC \times y} \times 100$$

BW_{x-y} = mean body weight at weighing prior to day x

BW_x = body weight on day x

FC = food consumption from day x-y to day x

y = interval in days between weighings

Group mean food consumption data are presented in Table 5 below:

TABLE 5
Group Mean Food Consumption in Male and Female Mice Given Dazomet in the Diet for 78 Weeks[a]

Food consumption (g/mouse/day)

Week of Study	Males				Females			
	0	20	80	320	0	20	80	320
1	6.8	6.6	6.9	6.8	7.4	7.9	7.8	7.8
13	5.9	7.0	7.2	7.4	7.2	9.6	8.9	9.1
53	7.7	7.4	9.0	9.0	9.0	10.1	10.4	10.2
78	6.1	8.0	7.1	7.7	7.5	9.3	9.1	8.6

[a]data taken from Tables 001-004 and 008-011, pages 49-52 and 56-59 of the report.

As shown in Table 5 , group mean food consumption in treated male and female mice was not significantly decreased at any dose level over the course of the study. Food consumption was, however, noticeably increased in treated female mice at all dose levels, which is consistent with the observed increased body weight and weight gain in these mice as compared to the controls. Food consumption was slightly increased in male mice at the 80 and 320ppm dose level.

Food efficiency for the study in male and female mice is summarized in the following table (Table 6):

TABLE 6
Group Mean Food Efficiency in Male and Female Mice Given Dazomet in the Diet for 78 Weeks[a]

Food efficiency (b.w. gain/food consumed)

Week of Study	Males 0	20	80	320	Females 0	20	80	320
1	3.1	3.0	3.4	1.8[c]	3.5	3.1	3.0	2.3[c]
7	0.7	0.3	0.6	1.4[c]	1.3	0.2[c]	0.1[c]	0.5[c]
13	1.8	0.7[c]	2.0	0.7[c]	0.3	0.2	0.6	1.0
1-13[d]	1.4	1.0	1.1	0.8	0.9	0.9	1.0	0.9

[a]data taken from Tables 043-044 and 050-051, pages 91-92 and 98-99 of the report.
[b]$p < 0.05$ vs control; [c]$p < 0.01$ vs control.
[d]calculated from group mean food efficiency for weeks 1-13.

Food efficiency in male mice from the 320ppm dose group was significantly decreased during weeks 1 and 13 of the study by 42 and 62%, respectively, and for weeks 1-13 of the study, food efficiency in male mice was decreased by 43%.

In female mice, significant decreases in food efficiency were observed for week 1 at the 320ppm dose level, and for all dose levels at week 7. Overall food efficiency was, however, not significantly decreased in treated female mice for weeks 1-13 of the study.

The combined observations of decreased group mean body weight, body weight gain, and food efficiency with no change in food consumption supports the conclusion of test article toxicity in male mice. In female mice, the combined observations of body weight, body weight gain, food consumption, and food efficiency do not conclusively show test article toxicity. Although food efficiency was decreased in female mice at the start of the study and was accompanied by decreases in body weight gain, overall food efficiency was unaffected in female mice, and there were no significant decreases in body weight or body weight gain in this sex at any dose level.

D. Intake of Dazomet

The group mean intake of dazomet for male and female mice over the course of the study is summarized in the following table (Table 7):

TABLE 7

Group Mean Dietary Intake of Dazomet in Male and Female Mice Over 78 Weeks [a]

Dose Group (ppm)	Average Intake (weeks 1-78) (mg/kg/day) males	females
0	0	0
20	4.58 (3.94)	6.59 (5.67)
80	17.91(15.59)	24.56 (21.37)
320	76.0 (69.92)	103.2 (94.95)

[a]data calculated from Tables 057-060 and 064-067 , pages 105-108 and 112-115 of the report.

Group mean intake of dazomet across all dose groups was supplied by the registrant and is summarized above for the study duration. Based upon the finding that dietary concentration of test article at 20 ppm was 14% below nominal 13% below nominal at 80ppm, and 8% below nominal at 320 ppm (see page 4, above), the actual amount ingested is shown in parentheses above in the table. Regardless of this correction, it is apparent that female mice received between a 35-43% greater amount of test article than male mice over the course of the study, based upon an increased food consumption in treated female mice (Table 5, above).

E. Clinical Pathology

Mice were subject to inspection for palpable masses once a week when being observed for clinical signs of toxicity. Blood for hematological examination was obtained from all mice of the satellite groups at 52 weeks and from all surviving mice at 78 weeks. Blood was obtained following decapitation and subjected to differential blood count using Wright's stain.

As noted above in this review (page 6), there were no signs of clinical toxicity associated with test article administration. There was no significant occurrence of palpable masses in either male or female mice which appeared related to treatment with test article. No significant effects of test article on hematologic parameters was observed in either male or female mice (Tables 076-086, pages 123-134 of the report).

F. Organ Weights

The weight of the liver, kidneys, brain, adrenals, and testes was obtained at sacrifice for those mice scheduled for sacrifice. Relative organ weights were calculated using body weights of anesthetized mice at terminal sacrifice.

Organ weights which were observed to be significantly altered from control mice in the interim and terminal sacrifice groups are summarized below (Tables 8 and 9):

TABLE 8
Absolute and Relative Organ Weights in Male and Female Mice Given Dazomet in the Diet for 52 Weeks [a]

	Males				Females			
	0	20	80	320	0	20	80	320
No. mice	10	10	10	10	10	10	10	10
liver wt.	1.3±0.05	1.25±0.1	1.38±0.16	1.56±0.23 [c]	1.22±0.11	1.30±0.13	1.37±0.16 [b]	1.50±0.11 [c]
liver /b.w.	3.24±0.19	3.30±0.21	3.21±0.14	4.03±0.26 [c]	3.79±0.33	3.90±0.41	4.14±0.39	4.60±0.43 [c]
kidneys	0.63±0.03	0.57±0.04 [c]	0.59±0.05	0.56±0.03 [c]	0.42±0.02	0.45±0.08	0.44±0.03	0.45±0.02
kidney /b.w.	1.56±0.1	1.50±0.14	1.37±0.09 [c]	1.45±0.11	1.33±0.15	1.38±0.40	1.34±0.15	1.37±0.17
testes	0.22±0.05	0.24±0.01	0.24±0.01	0.24±0.01				
testes /b.w.	0.54±0.13	0.63±0.06 [b]	0.57±0.05	0.63±0.06				

Data taken from Table I, pages 475-476 of the report.
[b]p <0.05 vs control; [c]p <0.01 vs control.

At 52 weeks, group mean absolute liver weights were increased in female mice from the 80ppm dose group and in male and female mice from the 320ppm dose group. In female mice, absolute liver weight was increased by 12 and 23% in the 80 and 320ppm dose groups, respectively. In male mice, group mean absolute liver weight was increased by 20% in the 320ppm dose group. The liver:body weight ratio was also significantly increased in male and female mice from the 320ppm dose group.

In male mice, group mean absolute kidney weight was decreased by 10% at the 20 and 320ppm dose level, while the kidney : body weight ratio was decreased significantly in male mice only at the 80ppm dose level, where absolute kidney weight was unaffected.

Group mean absolute testicular weight was unaffected in male mice, but the testes : body weight ratio was increased significantly (16%) at the 20ppm dose.

TABLE 9
Absolute and Relative Organ Weights in Male and Female Mice Given Dazomet in the Diet for 78 Weeks [a]

	Males				Females			
	0	20	80	320	0	20	80	320
No. mice	50	49	47	50	48	50	50	48
liver wt.	1.48±0.46	1.41±0.44	1.49±0.42	1.70±0.23 [b]	1.23±0.13	1.30±0.20	1.36±0.20 [b]	1.54±0.17 [c]
liver /b.w.	3.85±1.67	3.81±1.44	3.93±1.19	4.72±0.60 [c]	4.01±0.48	4.18±0.72	4.18±0.89	5.05±0.47 [c]
kidneys	0.71±0.05	0.65±0.04 [c]	0.63±0.05 [c]	0.60±0.04 [c]	0.46±0.03	0.47±0.03 [b]	0.47±0.03 [b]	0.49±0.03 [c]
kidney /b.w.	1.82±0.19	1.75±0.18	1.65±0.14 [c]	1.68±0.13 [c]	1.50±0.21	1.51±0.17	1.46±0.22	1.61±0.18 [b]
testes	0.22±0.01	0.22±0.02	0.22±0.02	0.22±0.01				
testes /b.w.	0.57±0.06	0.60±0.06	0.59±0.06	0.62±0.06 [c]				

Data taken from Table II, page 477-478 of the report.
[b]p <0.05 vs control; [c]p <0.01 vs control.

At 78 weeks, group mean absolute liver weight was significantly increased by 15, 10, and 25% in male mice from the 320ppm dose group, and female mice from the 80 and 320ppm dose groups, respectively. Liver : body weight ratio was also significantly increased in male and female mice at the 320ppm dose level by 22 and 25%, respectively. While group mean absolute kidney weight was significantly decreased in male mice at all dose levels tested, mean kidney weight was significantly increased in female mice, but only by 2-6%. The testes : body weight ratio was also significantly increased in male mice at the 320ppm dose level, but no change in absolute group mean testes weight was observed. A significant increase was also noted in absolute brain weight at the 20 and 320ppm dose levels and adrenal weight in male mice at the 320ppm dose level.
Of interest is the dose-related trend in increased liver weights in female mice (which was also observed at 52 weeks in satellite mice) and the dose-related trend in decreased kidney weights in male mice (which was not apparent at 52 weeks).

G. Macroscopic Observations

All mice surviving to the end of the study were killed by decapitation under CO_2 anesthesia. Gross necropsy was performed on all mice sacrificed at study termination and mice which died and/or were sacrificed in extremis during the study.

According to the registrant (page 479 of the report, Table III), there were no treatment related macroscopic findings in mice examined from the interim (52 week) sacrifice.

Treatment related macroscopic pathology was evident in the liver of male and female mice sacrificed at 78 weeks. In male mice, the incidence of liver masses was increased from 8/50 in control mice to 8/50, 17/50, and 11/50 in the 20, 80, and 320ppm dose groups, respectively. In female mice, the incidence of this same lesion was increased from 2/50 in controls to 8/50 at the 320ppm dose level (no increase at the 20 or 80ppm dose level). In addition to the increased incidence of liver masses in female mice, there was also an increase in foci of discoloration in female mice (incidence: 2/50, 4/50, 3/50, and 11/50 in control, 20ppm, 80ppm, and 320ppm, respectively).

There did not appear to be any other treatment associated macroscopic pathology.

H. Microscopic Observations

The following tissues were removed and preserved in 4% formaldehyde solution :

Digestive

- tongue
x salivary glands*
x esophagus*
x stomach*
x duodenum*
x jejunum*
x ileum*
x cecum*
x colon*
x rectum*
x liver*
x pancreas*
x gall bladder*

Respiratory

x trachea
x lungs*
- nasal cavity

Cardiovascular

x aorta*
x heart*
x bone marrow
x lymph nodes*
x spleen*
x thymus*

Urogenital

x kidneys*
x urinary bladder*
x testes*
x epididymides*
x seminal vesicle*
x prostate
x ovaries
x uterus*
- vagina

(cont.)

Neurologic	Glandular	Other
x brain*	x adrenals*	x bone (femur)
x peripheral nerve*	- lacrimal gland	x skeletal muscle
- spinal cord (3 levels)*	x mammary gland	x skin*
x pituitary*	x parathyroids*	x all gross lesions*
x eyes	x thyroids*	

*EPA guideline requirement "-" not examined

Tissues were prepared for microscopic examination by embedding in paraffin wax, cutting thin sections, and staining with hematoxylin and eosin. All preserved tissues of the control and high dose groups were examined, as were the liver, spleen, lung, kidneys, urinary bladder, and any unusual lesions of the low and mid dose groups. Tissues obtained from the low and mid dose groups of mice were stained additionally as follows: liver, Oil Red-O; spleen, Perl's Prussian Blue; kidneys and urinary bladder, PAS-reaction.

Note: All tissues were preserved as indicated in the guidelines (83-2).

1) Neoplastic Observations

At the interim sacrifice, there were no apparent treatment related findings of neoplastic lesions in male or female mice (Table V, pages 485-491 of the report). However, it should be noted that 1 male mouse from the 80ppm dose group was observed with a single hepatic adenoma and one from the 320ppm dose group was observed with 2 hepatic adenomas at this time point, whereas no neoplastic hepatic lesions were observed in female mice.

Data on neoplastic changes and tumor distribution in male and female mice from the terminal sacrifice are summarized in **Table 10** :

TABLE 10

Neoplastic Lesions in Male and Female Mice Given Dietary Dazomet for 78 Weeks[a]

	Males				Females			
Dose (ppm)	0	20	80	320	0	20	80	320
Liver								
No. of Animals Examined for Liver Tumors	50	50	50	50	50	50	50	49
Hepatic Adenoma	7[b] (14)[c]	5(10)	12 (24)	10 (20)	3 (6)	0 (0)	1 (2)	7 (14)
Hepatic Carcinoma	3 (6)	2(4)	2 (4)	2 (4)	0 (0)	1 (2)	1 (2)	0 (0)
Total (benign+ malignant)	10(20)[d]	7(14)	14(28)	12(24)	3(6)	1(2)	2(4)	7(14)
Pituitary								
No. of Animals examined for pituitary tumors	50	0	3	50	50	0	0	49
hyperplastic focus	0	0	0	0	4(8)	0	0	8(16)
adenoma	0	0	0	0	2(4)	0	0	1(2)

[a]data taken from Tables VI-VIII, pages 493-516 of the report.

[b]number of mice with specified lesion.

[c]percentage of mice with specified lesion.

[d]mice with benign and malignant tumors were separate animals in both sexes.

As shown in **Table 10** , there was an increase in the percentage of male mice with hepatic adenoma in the 80 and 320 ppm dose groups. An increase in the percentage of female mice with this lesion was also observed between controls and female mice in the 320 ppm dose group. In male mice, these increases were not striking (10% and 6% increase in the 80 and 320ppm dose groups, respectively) and the increase in hepatic adenoma for female mice was also not large (8%). However, trend analysis showed a significant trend for female mice with this lesion, suggesting an effect of treatment with test article.

Hyperplastic foci of the pituitary were also listed as a neoplastic finding in treated mice, and this lesion occurred in female mice only. The incidence of this lesion was increased from 8% in control mice to 16% in mice from the 320ppm dose group. However, as with the other lesions, the percentage increase between control and treated mice was small (8%).

2) Non-Neoplastic Observations

Several non-neoplastic pathologies were noted among treated male and female mice in this study. These included foci of cellular alteration in the liver, centrilobular lipid deposition in the liver, tubular lipid deposition in the kidney, lipofuscin deposition in the urinary bladder, and hemosiderosis in the spleen. Significant findings are summarized below (Table 11):

TABLE 11

Non-Neoplastic Lesions in Male and Female Mice Given Dietary Dazomet for 78 Weeks[a]

	Males				Females			
Dose (ppm)	0	20	80	320	0	20	80	320
Liver								
No. of Animals examined	50	50	50	50	50	50	50	50
foci of cellular alteration								
basophilic	4[b](8)[c]	9(18)	5(10)	10(20)	1(2)	3(6)	4(8)	13(26)

(cont.)

	Males				Females			
Dose (ppm)	0	20	80	320	0	20	80	320
Liver								
No. of Animals examined	50	50	50	50	50	50	50	50
lipid deposition								
minimal	14(28)	7(14)	12(24)	10(20)	2(4)	4(8)	8(16)	28(56)
slight	1(2)	0(0)	1(2)	17(34)	1(2)	0(0)	0(0)	2(4)
moderate	0(0)	0(0)	0(0)	14(28)	0(0)	0(0)	0(0)	0(0)
marked	0(0)	0(0)	0(0)	8(16)	0(0)	0(0)	0(0)	0(0)
Kidneys								
No. of Animals examined	50	50	50	50	50	50	50	50
tubular lipid deposition								
minimal	18(36)	41(82)	4(8)	0(0)	0(0)	0(0)	0(0)	0(0)
slight	32(64)	2(4)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
focal mononuclear cell infiltration	17(34)	13(26)	2(4)	2(4)	16(32)	13(26)	12(24)	7(14)
Urinary Bladder								
No. of Animals examined	50	50	50	50	50	50	50	50
lipofuscin deposition								
minimal	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	4(8)	12(24)
slight	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	37(74)

(cont.)

	Males				Females			
Dose (ppm)	0	20	80	320	0	20	80	320
Spleen								
hemosiderin deposition								
minimal	3(6)	5(10)	9(18)	14(28)	9(18)	13(26)	9(18)	2(4)
slight	0(0)	0(0)	0(0)	26(52)	24(48)	22(44)	17(34)	1(2)
moderate	0(0)	0(0)	1(2)	10(20)	13(26)	14(28)	18(36)	6(12)
marked	0(0)	0(0)	0(0)	0(0)	3(6)	1(2)	5(10)	30(60)
severe	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	10(20)

[a]data taken from Tables A-E, pages 466-469 of the report.

[b]number of mice with this lesion.

[c]percent of mice with this lesion.

In the liver, foci of cellular alteration were increased in incidence in both male and female mice, primarily at the 320ppm dose level, where the incidence in male mice increased from 8% to 20%, and the incidence in female mice increased from 2% to 26%.

Centrilobular lipid deposition was also observed in increased incidence and severity in both sexes, again primarily at the 320ppm dose level, and primarily in male mice. As shown above, the number of male mice demonstrating moderate and severe lipid deposition was greatly increased at the 320ppm dose level. The number of female mice with minimal and slight lipid deposition was also greatly increased at the 320ppm dose level. The increased incidence of lipid deposition was considered contributory to the increased absolute liver weight observed in male and female mice at this dose level.

In contrast to that observed in the liver, lipid deposition in the kidney was decreased with increasing dose of test article in male mice (where this lesion was observed). The decreased absolute kidney weight observed at study termination in male mice was considered to be related to the decreased lipid deposition.

Increased incidence of lipofuscin deposition was observed in female mice only at the 320ppm dose level. The degree of this deposition was scored as minimal and slight in all cases observed.

Hemosiderin deposition in the spleen was increased in both treated male and female mice. In male mice, there was an increased incidence of minimal hemosiderin deposition at the 320ppm dose level, while there was an increased severity of this deposition in male mice at the 320ppm dose level, with 52 and 20% demonstrating slight and moderate hemosiderin deposition. In female mice, there was an increase primarily in the percentage of mice with marked and severe hemosiderin deposition at the 320ppm dose level. Sixty and 20% of mice at this dose level

demonstrated marked and severe hemosiderin deposition.

The non-neoplastic lesions of centrilobular lipid deposition in the liver, lipofuscin deposition in the urinary bladder, and hemosiderin deposition in the spleen were also observed in increased incidence in male and female mice from the interim sacrifice groups at the 320ppm dose level. In addition, male mice at the 80ppm dose level showed increased incidence of these lesions at 52 weeks compared to concurrent controls.

III. DISCUSSION

The present study was undertaken in order to assess the carcinogenic potential of dazomet in male and female B6C3F1 Crl/Br mice. The study was conducted from April 23, 1986 to November 5, 1987. Mice received dietary levels of 0ppm, 20ppm (3.94 mg/kg/day in males, 5.67 mg/kg/day in females), 80ppm (15.59 mg/kg/day in males, 21.37 mg/kg/day in females), and 320ppm (69.92 mg/kg/day in males, 94.95 mg/kg/day in females). Mice received test article for either 78 weeks (main study group; 50 mice/sex/dose) or for 52 weeks (satellite group; 10 mice/sex/dose). Mice were monitored for treatment related effects on mortality, body weight gain, food consumption, palpable masses, and clinical signs of toxicity. Satellite groups of mice were sacrificed at 52 weeks and subjected to hematologic analysis (differential blood count) and gross necropsy, as well as histopathologic analysis of selected tissues and organs. Mice in the main study were sacrificed at 78 weeks and subjected to hematologic analysis and complete gross necropsy and histopathologic examination. Tissues were examined for both potential neoplastic and non-neoplastic changes related to treatment with dazomet.

Mortality in both treated male and female mice was not significantly altered from control at any dose level of dazomet tested. No significant clinical toxicity was observed in either male or female mice as a result of treatment with dazomet.

Significant decreases in group mean absolute body weight were observed in male mice at the 320ppm dose level, while significant increases in group mean body weight were observed in female mice from the 20ppm and 80ppm dose groups compared to concurrent controls. In male mice from the 320ppm dose group, body weight decreases of 9, 11, and 10% were observed at weeks 13, 25, and 78 of the study, while female mice from the 20 and 80ppm dose groups showed increased mean body weight between 4-10% from weeks 13-53 of the study. Body weight gain was also significantly decreased in male mice over the course of the study. Group mean body weight gain in male mice from the 320ppm dose group was decreased to 66% of control for weeks 1-13 of the study, and was decreased to 78% of control for the study duration (weeks 1-78). While a decrease in body weight gain was also observed in male mice from the 20ppm dose group (decreased to 81% of control for weeks 0-13), this decrease did not persist for the duration of the study, and thus the effect at the high dose on absolute body weight and body weight gain can be regarded as treatment related. Female mice did not show any decrement in body weight gain over the course of the study.

Food consumption was largely unaffected in male mice for the course of the study (slightly increased at the 80 and 320ppm dose levels), but was increased between 15-23% in those groups

of treated female mice which showed increased absolute body weight during the study. In contrast to food intake, food efficiency was decreased by 43% in male mice from the 320ppm dose group for weeks 1-13 of the study, but was unchanged in female mice for this period of the study. The combined observations of decreased body weight gain and food efficiency in male mice supports the conclusion of test article toxicity at the 320ppm dose level for male mice. There was no evidence of test article toxicity in female mice from reported changes in body weight and food consumption, despite the observation (Table 7, page 11 of DER) that female mice received a 35-43% greater dose of test article across all dose groups than male mice.

The incidence of palpable masses was not significantly different among control and treated male and female mice. Organ weights were, however, significantly affected in male and female mice at both 52 And 78 weeks. At 52 weeks, liver weight in male mice from the 320ppm dose group was elevated by 20% in comparison to control mice, while liver weight in female mice from the 80 and 320ppm dose groups was elevated by 12 and 23%, respectively. Liver : body weight ratio was also significantly elevated in male and female mice at the 320ppm dose level.

Kidney weight at 52 weeks was significantly decreased in male mice by 10% at the 20 and 320ppm dose levels, while the testes : body weight ratio was significantly increased in male mice at the 20ppm dose level. The toxicological significance of decreased kidney weight is not clear, although a dose-related decreased incidence of tubular lipid deposition was observed in kidneys from male mice (Table 11, page 17 of DER) which could account in part for the decreased kidney weight. The increased testes : body weight ratio in male mice at the 20ppm dose level is assumed to be unrelated to treatment with dazomet.

At 78 weeks (terminal sacrifice), there were similar changes in organ weights as those observed at 52 weeks. Liver weight was increased by 15% in male mice at the 320ppm dose level, and by 10 and 255 in female mice at the 80 and 320ppm dose level. Liver : body weight ratio was also increased in both male and female mice at the 320ppm dose level 22 and 25%, respectively.

Kidney weight showed a dose-related decrease from 8-15% at 78 weeks in male mice, while a slight (2-6%) increase in kidney weight was observed in female mice at all dose levels. Testes : body weight ratio was again increased in male mice, but only at the 320ppm dose level. The absence of corresponding pathology in the testes does not support the idea of testicular toxicity, and the increased ratio is likely the result of decreased body weight in male mice at 78 weeks.

It should be noted that for organ weights, dose-related trends were apparent for the increase in liver weight in female mice, and for the decrease in kidney weight in male mice.

Macroscopic pathology was not evident in male and female mice at 52 weeks. At 78 weeks, increased incidence of liver masses was observed in male mice at the 80 and 320ppm dose levels (17/50 mice and 11/50 mice vs 8/50 mice in controls, an increase of 112 and 37%) and female mice at the 320ppm dose level (8/50 mice vs 2/50 mice at 0ppm, an increase of 300%). Foci of discoloration were also observed in increased incidence in female mice at all doses, although the greatest increase was observed at the 320ppm dose level, where 11/50 mice were observed with this lesion compared to 2/50 control mice, an increase of 450%. These lesions, especially at the 320ppm dose level, are considered an effect of treatment with test article.

The effects of dazomet administration on the incidence of neoplastic lesions in male and female mice was manifested primarily by an increase in liver adenoma in male and female mice, and an increase in pituitary hyperplastic foci in female mice. At 52 weeks, 1 male mouse from the 80ppm dose group was observed with a single hepatocellular adenoma, while 1 male mouse from the 320ppm dose group was observed with 2 adenomas. Hepatocellular adenoma was also observed

in increased incidence in male mice at 78 weeks, from an incidence of 14% in control mice to 24 and 20% in mice from the 80 and 320ppm dose groups, respectively. Female mice were observed with increased incidence of this lesion at the 320ppm dose level (14% incidence vs 6% in controls), a statistically significant positive trend (p=0.0475 by Cochran-Armitage test). Pituitary hyperplastic foci were also observed to double in incidence between control female mice and those from the 320ppm dose level (8% to 16%). It should be noted that while the increase in hepatocellular adenoma the effect itself is not dramatic. Hepatic carcinoma was not increased in incidence in treated male or female mice in this study.

A variety of non-neoplastic lesions were observed in increased incidence in treated male and female mice, including foci of cellular alteration in the liver, centrilobular lipid deposition, lipofuscin deposition in the urinary bladder (female mice only), and hemosiderin deposition in the spleen. Tubular lipid deposition in the kidney was observed to decrease in incidence with increasing dose of dazomet in male mice, which supports in part the decreased organ weight observed in this sex of treated mice. A summary of these lesions follows:

1) Basophilic foci of cellular alteration in the liver were increased from an incidence of 8% in control male mice to an incidence of 20% in mice from the 320ppm dose group. In females, an increase from 2% in controls to 26% at the 320ppm dose was observed. A dose-related trend for the incidence of this lesion was also apparent in female mice (Table 11, page 17 of DER).

2) Centrilobular lipid deposition in the liver was increased in incidence and severity in male mice. The number of male mice graded as having moderate and marked lipid deposition was increased at the 320ppm dose level. No male mice were observed with this grading at lower doses of dazomet. The incidence of this lesion but not the severity was increased in female mice at the 320ppm dose level.

3) Tubular lipid deposition in the kidney was decreased in a dose-related manner in male mice. No lesion of this type was observed in female mice.

4) Lipofuscin deposition in the urinary bladder was increased in incidence and severity in female mice at the 320ppm dose level. Virtually no lipofuscin deposition was observed at lower doses of dazomet.

5) Hemosiderin deposition was increased in incidence and severity in male mice. Minimal deposition was observed in 6% of male mice at 0ppm, and in 28% of male mice at the 320ppm dose level. At the 320ppm dose level, 52 and 20% of mice were observed with slight and moderate hemosiderin deposition, in comparison to 0 and 2% of male mice observed with this grade of hemosiderosis at the 80ppm dose level.

In female mice, an increased incidence of mice with marked and severe hemosiderin deposition was observed (60 and 20%, respectively) at the 320ppm dose level. Ten and 0% of female mice were graded with marked and severe hemosiderosis at the 80ppm dose level.

The present study supports the conclusion of limited carcinogenicity of dazomet in male and female mice. This is based upon the observation of increased incidence of hepatocellular adenoma

in male and female mice at 320ppm dazomet. A statistically significant positive trend was observed for this lesion in female mice only. Basophilic foci were found to be significantly increased in female mice when analyzed by Fisher's exact test and the Cochran-Armitage test. Pituitary hyperplastic foci were doubled in incidence between control and high dose female mice.

IV. CONCLUSIONS

Technical Dazomet was administered to male and female B6C3F1 mice in the diet for 78 weeks at doses of 0ppm, 20ppm (3.9 mg/kg/day in males, 5.7 mg/kg/day in females), 80ppm (15.6 mg/kg/day in males, 21.4 mg/kg/day in females), and 320ppm (69.9 mg/kg/day in males, 95.0 mg/kg/day in females). Decreased body weight, body weight gain, and food efficiency were observed in male mice from the 320ppm dose group. Increased liver weight and liver : body weight ratio was observed in male and female mice from the 320ppm dose group sacrificed at 52 and 78 weeks. Incidence of hepatocellular adenoma was increased in male and female mice from the 320ppm dose group, and in male mice from the 80ppm dose group. A statistically significant trend for increased hepatocellular adenoma and basophilic foci of cellular alteration in the liver was reported in female mice.

Based on the effect of test article on body weight gain in male mice, liver weight in male and female mice, and incidence of basophilic foci of cellular alteration in livers of male and female mice during weeks 0-78 of the study, it appears that the MTD was achieved for dazomet.

The data in this study support the conclusion of limited evidence of carcinogenicity for technical dazomet, based upon the occurrence of increased incidence of hepatocellular adenomas in male and female mice at 320ppm dazomet.

The No Observed Effect Level (NOEL) = 20 ppm

The Lowest Observed Effect Level (LEL) = 80 ppm (increased liver masses in male mice at 78 weeks; increased liver weight in female mice at 78 weeks).

The Maximum Tolerated Dose (MTD) = 320 ppm (decreased body weight gain in male mice during weeks 0-13; increased liver weight and lipid deposition in male and female mice at 78 weeks; increased incidence of basophilic foci of cellular alteration in males and females at 78 weeks).

V. CLASSIFICATION

Core minimum

This study satisfies the guideline requirements (83-2) for a carcinogenicity study in mice.

Reviewed by: Timothy F. McMahon, Ph.D. 10/16/91
Section I, Toxicology Branch II (H7509C)
Secondary Reviewer: Stephen C. Dapson, Ph.D. Stephen C. Dapson 10/16/91
Section I, Toxicology Branch II (H7509C)

008736

Data Evaluation Report

Study type: Developmental Toxicity- Teratology
Species: rabbit
Guideline: 83-3

EPA ID Numbers: MRID number: 920280-11
Caswell No: 840
HED Project No: 1-2243

Test material: tetrahydro-3,5-dimethyl-2 H-1,3,5-thiadiazine-2-thione

Synonyms: Dazomet

Study number(s): 87/5010

Testing Facility: Department of Toxicology
BASF Ludwigshafen, W. Germany

Sponsor: Dazomet Task Force

Title of report: Prenatal Toxicity of Dazomet in Rabbits

Author(s): Dr. Merkle

Study Completed: July 15, 1980

Conclusions: Administration of Dazomet technical to pregnant female American Dutch rabbits resulted in maternal toxicity at 25, 50 and 75 mg/kg/day. There was evidence of developmental toxicity of dazomet at the dose levels tested, but insufficient evidence was presented to conclusively demonstrate developmental toxicity.

Maternal NOEL= 12.5 mg/kg/day
Maternal LOEL= 25 mg/kg/day (decreased body weight gain on days 0-20 [study #2]).

Tentative Developmental toxicity NOEL = 12.5 mg/kg/day
Tentative Developmental toxicity LEL = 25 mg/kg/day (increased resorptions and resorptions/dam)

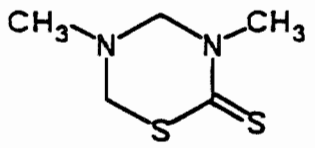
CLASSIFICATION Core supplementary

This study does not satisify the guideline requirements (83-3) for a teratogenicity study in rabbits and cannot be upgraded. The registrant is asked to repeat this study at appropriate dose levels using an adequate number of dams to produce at least 12 litters/dose group.

I. MATERIALS and METHODS

A. Test Material: tetrahydro-3,5-dimethyl-2 H-1,3,5-thiadiazine-2-thione
purity: 98-100% a.i.
description: white solid (powdery)
test substance # 79/41 and 79/41-1

structure:



B. Vehicle: aqueous carboxymethylcellulose (Tylose®, HOECHST AG)

C. Compound Stability and Homogeneity: The registrant stated in both reports (pages 22 and 194) that stability of dose suspensions was not carried out "since the suspensions were prepared freshly each day and administered shortly afterward."
Note: In the Chronic Toxicity study in Dogs (MRID # 419677-01), dazomet was found to be unstable in feed, declining in concentration by approximately 30% within one hour of preparation.

D. Test Animals: Species: Himalayan Rabbit, strain Chbb:HM (outbred), female (virgin)

Source: DR. K. THOMAE, GmbH, Biberach, FRG.
Age: 20-41 weeks (at beginning of randomization)
Weight: 1.89-2.43 kg; mean wt. 2.19kg (day 0 of pregnancy)

E. Animal Husbandry:

A total of 62 female rabbits were used in report #1, while 60 female rabbits were used in report #2. Rabbits were housed individually in wire cages (type UNO HD II, Becker & Co., FRG) in a temperature (21-24 °C, study #1; 22± 2 °C, study #2) and humidity (52-84%, study #1; 55±5%, study #2) controlled room with a 12 hour light/dark cycle). Rabbits were individually identified by ear tatoo, but were apparently not numbered until the end of the study (page 16 and 189 of the report). Food (Ssniff K complete diet for rabbits produced by Plange Kraftfutterwerk Soest GmbH, FRG) and tap water were available ad libitum. Food was provided as approximately 130 g/ rabbit/day. Acclimation of rabbits to the study environment was not specified. No significant deviations were reported in environmental conditions during the study, although records were not provided.

F. Experimental Design and Dosing:

Dazomet Technical was administered as a suspension in 0.5% CMC vehicle by gavage to female rabbits on gestation days 6 through 18 inclusive in order to assess developmental toxicity of this chemical. Doses for study #1 were selected based upon acute toxicity studies in which doses of 100, 147, and 215 mg/kg were used , while doses for the second study were selected based upon report # 83/037, in which a maternal and developmental NOEL was apparently not attained. Dose volume was 5ml/kg. Dose volume was based upon body weight obtained on day 6 p.i.

Doses and numbers of rabbits tested at each dose level are as follows:

Study # 1	0 mg/kg/day:	11 rabbits
	25 mg/kg/day:	13 rabbits
	50 mg/kg/day:	13 rabbits
	75 mg/kg/day:	14 rabbits
Study # 2	0 mg/kg/day:	15 rabbits
	6.25 mg/kg/day:	15 rabbits
	12.5 mg/kg/day:	15 rabbits
	25 mg/kg/day:	15 rabbits

G. Mating

One hour prior to insemination, rabbits were injected with 40 I.U. of Primogonyl® (chorionic gonadotropin) dissolved in 1ml of physiological saline into the ear vein. The day of insemination was designated as gestation day 0. The source of sperm used in these studies was not specified.

H. Statistical Analysis:

A copy of the statistical tests used in these studies and the purposes for which they were employed is appended to this report.

I. Compliance:

A signed statement of Compliance with Good Laboratory Practice Standards was provided. This study was conducted prior to 40 CFR 160, but was "performed in the spirit of GLP" (page 3 of the original report; this statement does not appear in the reformatted report).

A signed statement of Data Confidentiality Claims was provided.

A signed statement of Quality Assurance was not provided for either study.

A signed statement of Flagging of Studies for Potential Adverse Effects was not provided for either study.

II. OBSERVATIONS and RESULTS:

A. Maternal Toxicity

1. Mortality

All animals were observed daily for signs of mortality. Animals which died were dissected on the day of death or the following weekday and subject to gross pathological examination, including examination of the uterus for implantations.

There were no deaths in study # 2. In study #1, two dams in the 75 mg/kg/day dose group were found dead (Table 067, page 127 of the report). Cause of death for one dam was probably related to gavage error (page 39 of the report), as the animal dies shortly afer the 7th treatment. The other dam showed severe diarrhea from day 11 post-implantation, and died on day 17 post-implantation.

2. Clinical Toxicity

Animals were observed daily for signs of clinical toxicity, except on weekends or when there was no treatment. Note: This raises the question of whether the rabbits received all doses of dazomet, if in fact there was no treatment on weekends.

In study #1, clinical toxicity was observed in dams from the 50 and 75 mg/kg/day dose groups. At 50 mg/kg/day, one dam was observed with severe diarrhea from day 7 post-insemination (p.i.) , and apathy. This dam was sacrificed on day 26 p.i. due to severe weight loss and the development of purulent conjunctivitis. A second dam was observed with severe diarrhea from day 14 p.i. to the end of the study. At 75 mg/kg/day, diarrhea was observed in 2 dams from days 7 and 11 p.i., while apathy was observed in 2 other dams throughout the treatment period. Two of these dams died during the treatment period.

In study #2, there were no apparent signs of clinical toxicity observed. One dam at the 25 mg/kg/day dose level was treated for purulent conjunctivitis from day 2 p.i. until day 6 p.i., and again on p.i. days 24-25.

3. Body Weight:

Body weights were recorded in study #1 three times a week, and additionally on the day of insemination and again on p.i. days 6, 18, and 30. In study #2, weights were recorded 3 times a week and again on the day of insemination and on days 6 and 29 p.i. Group mean body weights, group mean body weight gain, and individual body weight data were provided. Group mean body weight gain is shown in Table 1a for study #1, and group mean body weight gain for study #2 is shown in Table 1b .

TABLE 1a

Group Mean Body Weight Gains (g) in Dazomet Technical-Treated Rabbits[a]

Study Interval (days)	Dose groups (mg/kg/day)				
	0	0[b]	25	50	75
0-6	57.1	83.6	48.0	47.6	24.0
6-19	67.6	99.4	-35.8	-67.6	-111.3
19-30	237.5	128.6	185.4	115.0	152.0
0-30	362.3	311.6	197.6	95.0	64.7

Animals which were non-pregnant were excluded from analysis.

[a]Data calculated from Tables 007-009, pages 77-79 of original report; [b]vehicle control

From days 0-6 and 6-19 of the study, the data show an apparent dose-related decrease in body weight gain for treated dams vs vehicle controls. Body weight gain for study days 19-30 did not appear decreased in treated dams vs controls. Overall body weight gain for study days 0-30 also showed a dose-related decrease of 36, 69, and 79% in the 25, 50, and 75 mg/kg/day dose groups vs vehicle control. Note: Tables 007-014 missing from reformatted study.

TABLE 1b

Group Mean Body Weight Gains (g) in Dazomet Technical-Treated Rabbits[a]

Study Interval (days)	Dose groups (mg/kg/day)			
	0[b]	6.25	12.5	25.0
0-6	-7.0	-6.8	8.3	-21.8
6-20	10.4	69.0	54.1	-56.0
20-29	116.3	209.0	102.4	97.6
0-29	119.7	271.2	164.8	19.8

Animals which were non-pregnant were excluded from analysis.

(Table 1b, cont.)

[a]Data from Tables 007-009, pages 234-236 of the report.
[b]vehicle control

Effects on body weight gain in study #2 occurred primarily in the 25 mg/kg/day dose group from study days 0-20. These decreases in body weight gain resulted in a decrease of 83% for overall body weight gain in the 25 mg/kg/day dose group vs vehicle control for the study duration (days 0-29).

4. Food consumption

Food consumption was monitored daily in both studies. The amount of food consumed was determined by subtraction of that portion not eaten each day from the amount offered. Data on group mean food consumption and individual food consumption were provided by the registrant. Food consumption data for study 1 is summarized in the following Table (Table 2). Food consumption was unaffected in study #2.

TABLE 2

Food Consumption (grams) in Dazomet Technical-Treated Rabbits[a]

Study day	Dose Group (mg/kg/day)			
	0[b]	25	50	75
1	84.47	91.17	92.40	84.98
6	87.52	94.48	97.28	85.55
7	86.20	78.34	75.94	34.61
12	92.95	68.96	67.97	41.85
15	81.50	48.74	58.50	39.23
19	86.96	52.85	62.31	47.62
23	106.86	84.99	103.35	107.44
28	105.89	104.36	103.60	89.17

[a]data taken from Table 001, page 69 of registrant report; [b]vehicle control.

As shown in Table 2a , food consumption was not affected during the first 6 days of treatment, but by day 7, a 60% decrease in food consumption was observed in the 75 mg/kg/day dose group. From study days 12-19, decreases in food consumption between 25-50% were observed in all treated groups of dams. According to statistical analysis performed by the registrant (page 70 of the

report), significant differences were found only in the 75 mg/kg/day dose group for the study intervals days 6-9, 10-14, and 15-19. However, it is apparent that decreases were observed at all dose levels during this period of the study in study #1.

No apparent effects of test article administration on food consumption were observed in study #2.

5. Gross Pathology

Any rabbits which died, appeared moribund or showed signs of early termination of pregnancy were submitted for gross necropsy. On day 29 (study #2) or day 30 of gestation, all surviving does were terminated by intravenous barbiturate overdose. The abdomen was opened and the uterus excised with ovaries. The uterus was removed intact and weighed before opening. The uterus was then opened, fetuses and resorptions removed, and each implant noted. Abdominal and thoracic viscera were examined in maternal rabbits and any gross anatomical changes recorded.

Fetuses were delivered by Cesarean section. The sex, length, and weight of fetuses and placentas were determined. All fetuses were eviscerated and examined macroscopically. Subsequent to pathological examination, fetuses were X-rayed for determination of skeletal abnormalities. Heads were fixed additionally in Bouin's solution and processed according to the method of Wilson.

i) Gross Observations

Necropsy findings on individual female rabbits were not provided. Only summaries of any dams displaying abnormal pathology were provided.

According to the registrant (pages 41 and 211), there were no apparent gross pathological changes associated with test article treatment in maternal rabbits. However, pathological data on at least those rabbits which died during test article administration should have been provided in order to assess any test article related pathology in these animals.

ii) Histopathologic Observations

No histological data were provided on maternal tissues in this report.

iii) Organ Weights

The weight of the uterus was provided for each maternal rabbit. According to the registrant (Table 068, page 128 of the report), group mean uterine weight in dams from the 50 and 75 mg/kg/day dose groups (study #1) was significantly decreased ($p < 0.01$) in relation to controls. Uterine weight decreased from a mean value of 243.67g in vehicle controls to 60.7 and 62.55g in the 50 and 75 mg/kg/day dose groups, respectively. In study #2, uterine weights were unaffected at any dose level.

iv) Cesarean Section Observations

Table 3a : Cesarean Section Observations (Study #1)[a]

Dose (mg/kg/day):	0	0[b]	25	50	75
#Animals Assigned	11	11	13	13	14
#Animals Mated/ Inseminated	11	11	10	10	13
Pregnancy Rate (%)	100	100	77	77	93
Maternal Wastage					
#Died	0	0	0	0	2
#Died/pregnant	0	0	0	0	2
#Non pregnant	0	0	3	3	1
#Aborted	1	0	0	0	0
#Premature Delivery	2	2	1	0	0
Whole Litter Resorptions[c]	0	1	0	7	6
Total # of litters	8	8	9	3	5
Total Corpora Lutea	62	71	78	51	83
Corpora Lutea/dam[d]	5.6	6.4	7.8	5.1	6.3
Total Implantations	42	53	53	61	63
Implantations/Dam[e]	3.8	4.8	5.3	6.1	4.8
Total Live Fetuses	42	37	37	9	9
Live Fetuses/Dam	3.8	3.3	3.7	0.9	0.7
Total Resorptions	0	16	16	52	54

Table 3a (cont.)

Dose (mg/kg/day):	0	0[b]	25	50	75
Early	0	4	14	47	38
Intermediate	0	2	0	5	16
Late	0	1	2	0	0
Resorptions/Dam	0	0.6	1.6	5.2	4.1
Total Dead Fetuses Dead Fetuses/Dam	[no dead fetuses were reported]				
Mean Fetal Weight (gm)[f] (M + F)	48.0	47.0	47.4	43.3	44.1
% Preimplantation Loss (mean)	32.2	25.3	32.0	-19.0	24.0
% Postimplantation Loss (mean)	0	30.1	30.1	85.0	85.7
Sex Ratio (mean M/F)	3.1/2.1	2.8/1.7	2.4/1.6	1.6/1.3	1.2/0.6

[a]Data taken from Tables 067 and 078, pages 127 and 138 of report.

[b]vehicle control

[c]data taken from Tables 079-083, pages 140-144 of report.

[d,e]data recalculated from Table 078, page 138 of the report.

[f]data taken from Table 089, page 150 of the report.

It is noted that there were less than 12 litters/dose group as required for a teratology study in rabbits.

There were no apparent treatment related alterations suggestive of maternal toxicity, although the increase in the number of whole litter resorptions and decreased total number of litters in the 50 and 75 mg/kg/day dose groups may be suggestive of maternal toxicity.

Developmental toxicity was apparent at the 50 and 75 mg/kg/day dose levels in the form of a decrease in total live fetuses, live fetuses/dam, and increased resorptions in these dose groups vs controls. The number of early and intermediate resorptions was also increased at the 50 and 75 mg/kg/day dose levels. Fetal weight was not significantly different among the dose groups for the sexes combined, but mean female fetal weight was significantly decreased in the 50 and 75 mg/kg/day dose groups (Table 089, page 150 of the report). Post implantation loss was also greatly increased at the 50 and 75 mg/kg/day dose level, increasing to 85% at these 2 doses vs 30% in

controls. **Note:** The negative pre-implantation loss at 50 mg/kg indicates a problem with counting copora lutea in this dose group.

Table 3b : Cesarean Section Observations (Study #2)[a]

Dose (mg/kg/day):	0[b]	6.25	12.5	25
#Animals Assigned	13	15	15	15
#Animals Mated/ Inseminated	13	15	15	15
Pregnancy Rate (%)	77	80	100	87
Maternal Wastage				
#Died	0	0	0	0
#Died/pregnant	0	0	0	0
#Non pregnant	3	3	0	2
#Aborted	1	0	1	2
#Premature Delivery	1	0	2	1
Whole Litter Resorptions[c]	0	0	1	2
Total # of litters	8	12	11	8
Total Corpora Lutea	62	101	93	81
Corpora Lutea/dam[d]	6.2	8.4	6.2	6.2
Total Implantations	39	85	75	58
Implantations/Dam[e]	3.9	7.0	5.0	4.4
Total Live Fetuses	33	82	61	35
Live Fetuses/Dam	3.3	6.8	4.0	2.6

Table 3b (cont.)

Dose (mg/kg/day):	0[b]	6.25	12.5	25
Total Resorptions	6	3	12	23
Early	6	3	7	23
Intermediate	0	0	5	0
Late	0	0	0	0
Resorptions/Dam	0.6	0.25	0.8	1.7
Total Dead Fetuses	[2 dead fetuses were reported in the 12.5 mg/kg/day dose group]			
Dead Fetuses/Dam				
Mean Fetal Weight (gm)[f] (M + F)	40.2	38.9	41.0	39.6
% Preimplantation Loss (mean)	37.0	16.0	19.3	28.3
% Postimplantation Loss (mean)	15.0	3.5	18.6	39.6
Sex Ratio (mean M/F)	2.2/1.8	3.0/3.8	2.4/3.0	2.2/2.1

[a]Data taken from Tables 071 and 083, pages 297 and 309 of report.

[b]vehicle control

[c]data taken from Tables 072-075, pages 298-301 of report.

[d,e]data recalculated from Table 071, page 297 of the report.

[f]data taken from Table 083, page 309 of the report.

In study #2, there was an apparent indication of maternal and/or developmental toxicity from examination of the data in Table 3b, as total resorptions and resorptions/dam were increased at the 25 mg/kg/day dose level. The increase in resorptions/dam appeared to follow a dose-related trend. Of note were the low values for pregnancy rate and total implantations as well as the high value for pre-implantation loss in the control group, indicating a potential error in the timing of dosing (i.e. dosing prior to the completion of implantation).

In both study #1 and #2, there were insufficient numbers of litters in the control groups to provide a meaningful analysis of observations at cesarean section. In addition, the number of litters/dose group was insufficient at all doses in study #1 (at least 12 litters/dose group required by the guideline for teratology studies).

2. Developmental Toxicity

Following sacrifice of the fetuses, the abdomen and thorax of each fetus was opened for gross examination of organs before removal. The sex of the fetuses were determined, and sagittal sections made through the heart and kidneys.

Following internal examination, fetuses were X-rayed for examination of the skeletons. After X-ray, the heads of all fetuses were fixed in Bouin's solution and processed according to the method of Wilson.

TABLE 4a

Developmental Toxicity of Dazomet Technical (Study #1)[a]

Dose group (mg/kg/day)	0	0	25	50	75
Observations[a]					
#pups(litters) examined	42 (8)	37(8)	37 (9)	9(3)	9(5)
#pups(litters) affected					
anomalies	2(1)	1(1)	0(0)	1(1)	0(0)
variations and retardations	39(8)	31(8)	26(9)	5(3)	5(4)

[a] Data taken from Table 115, page 176 of registrant report.

Definitions of anomalies and variations were provided by the registrant (page 29) and were as follows:

anomalies: "changes which could be recorded and had progressed beyond the degree of retardation and variations."

variation: "changes which regularly occurred."

retardation: "delays in development compared with the norm at the time of the examination (cesarean section)."

a. External Malformations

According to the registrant, nonspecific external changes unrelated to treatment were observed in

all fetuses with external abnormalities, including control fetuses. Length and weight of female fetuses from the 75 mg/kg/day dose group appeared to be increased relative to control fetuses, along with placental weight. Pseudoankylosis was reported in 1 fetus from the vehicle control, and in 1 fetus from the 50 mg/kg/day dose group. No other data other than fetal weight and length were provided, although an apparent summary of external examination appears on page 45 of the report.

b. Visceral Malformations

Information on abdominal visceral examination of fetuses was provided in this study (tables 111-114, pages 172-175 of the report). Absence of the gall bladder was noted in two fetuses from untreated control, and in 1 fetus from the 50 mg/kg/day dose group. No other information was provided.

c. Skeletal Malformations

Information on examination of sternum and ribs was provided (Tables 103-109, pages 164-170 of the report). The most prevalent finding was bilateral accesory ribs and partially ossified sternebrae, which occurred in untreated, vehicle treated control, and 25 mg/kg/day fetuses to a much greater extent than in fetuses from the 50 and 75 mg/kg/day groups. Examination of apparent historical control data (Appendices 6-8, pages 60-62 of the report) did not shed any light on why this occurred.

TABLE 4b

Developmental Toxicity of Dazomet Technical (Study #2)[a]

Dose group (mg/kg/day)	0	25	50	75
Observations[a]				
#pups(litters) examined	42 (8)	37 (9)	9(3)	9(5)
#pups(litters) affected				
anomalies	2(1)	3(2)	3(2)	0(0)
variations and retardations	25(8)	73(12)	43(11)	23(8)

[a] Data taken from Table 108, page 334 of registrant report.

a. External Malformations

According to the registrant, nonspecific external changes unrelated to treatment were observed in all fetuses with external abnormalities, including control fetuses. Length and weight of pups were

unaffected among the dose groups (Tables 083 and 084, pages 309-310). Pseudoankylosis was reported in 2 fetuses from the 6.25 mg/kg/day dose group, and in 1 fetus from the 12.5 mg/kg/day dose group. No other data were provided.

b. Visceral Malformations

Information on abdominal and head visceral examination of fetuses was provided in this study (tables 101-107, pages 327-333 of the report). Absence of the gall bladder was noted in two fetuses from vehicle control, in 2 fetuses from the 6.25 mg/kg/day dose group, and in 1 fetus from the 12.5 mg/kg/day dose group. Anophthalmia (unilateral) was reported in 1 fetus from the 12.5 mg/kg/day dose group. No other information was provided.

c. Skeletal Malformations

Information on examination of sternum and ribs was provided (Tables 94-100, pages 320-326 of the report). The most prevalent findings were absent sternebrae (vehicle control and 6.25 mg/kg/day dose groups) and partially ossified sternebrae (6.25 and 12.5 mg/kg/day dose groups). These variations did not appear to show an increased incidence with dose, and were reported in lower incidence at the 25 mg/kg/day dose level. Examination of apparent historical control data (Appendices 6-8, pages 60-62 of the report) did not indicate clearly whether these changes in the control group fell within historical control range.

III. DISCUSSION

In the present study, the developmental toxicity of Dazomet technical was assessed by oral administation of the chemical at doses of 0, 6.25, 12.5, 25, 50, and 75 mg/kg/day to pregnant female Himalayan Rabbits on days 6-18 of gestation inclusive. These doses were used in 2 different studies conducted under apparently similar conditions. Doses of 0, 25, 50, and 75 mg/kg/day were used in the first study, and doses of 0, 6.25, 12.5, and 25 mg/kg/day were used in the second study. Daily observations were made for maternal toxicity of Dazomet technical, while body weights were recorded in study #1 three times a week, and additionally on the day of insemination and again on p.i. days 6, 18, and 30. In study #2, weights were recorded 3 times a week and again on the day of insemination and on days 6 and 29 p.i. On days 29 and 30 of gestation, surviving rabbits were killed by intravenous barbiturate overdose and were subjected to cesarean section to assess developmental toxicity of Dazomet technical.

Mortality was reported only in study #1, in which 2 dams from the 75 mg/kg/day dose group died during the study. The cause of death in these 2 rabbits was probably gavage error in one rabbit, and an undetermined cause in the second rabbit. Diarrhea was observed in 2 rabbits each from the 50 and 75 mg/kg/day dose groups, and was apparently contributory to the death of one rabbit at the 75 mg/kg/day dose group.

Changes in body weight gain of dosed rabbits were evident in study #1. A dose-related decrease in body weight gain was evident from study days 0-19, such that weight gain for the entire gestation period (days 0-30) was decreased 36, 69, and 79% in dosed rabbits at the 25, 50, and 75 mg/kg/day dose groups, respectively. In study #2, effects were seen primarily at the 25 mg/kg/day dose level from study days 0-20. In study #1, decreased food consumption was observed from days

7-19 of the study at all dose levels, which could explain the decrease in body weight gain, especially as no significant clinical symptoms other than diarrhea were reported. However, no significant decrease in food consumption was observed in study #2, where weight gain was decreased during study days 0-20 in the 25 mg/kg/day dose group of dams. These findings support the conclusion of maternal toxicity at the 25, 50 and 75 mg/kg/day dose levels, but are limited in scope, as food consumption in rabbits is not a sensitive indicator of toxicity. Body weight gain decrements in this study are believed to be due to test article toxicity.

The evaluation of observations made at cesarean section is hindered by the lack of an adequate number of litters per dose group (less than 12 at each dose level in both studies). In addition, the pregnancy incidence in control rabbits in study #2 (77%) is unacceptably low, as are the number of implantations relative to treated rabbits. Pre-implantation loss is also higher in controls then treated rabbits in this study.

In study #1, the total number of live fetuses and live fetuses/dam were decreased at the 50 and 75 mg/kg/day dose levels vs control. An increased number of resorptions was also observed at these 2 dose levels, while the number of resorptions in the 25 mg/kg/day dose group was similar to control. Post-implantation loss was also greatly increased in rabbits from the 50 and 75 mg/kg/day dose groups. These observations, while limited in their implication due to the inadequate number of litters, are believed to be the result of developmental toxicity.

Cesarean section observations in study #2 show increased resorptions in dams from the 12.5 and 25 mg/kg/day dose groups. The number of resorptions/dam also showed a dose-related increase. As with study #1, the implications of these results are limited due to inadequate numbers of litters.

The fetal toxicity of dazomet could not be properly evaluated, due to a lack of information from skeletal and visceral examinations. Examinations conducted on fetuses did not appear thorough enough. Specific information on each organ and tissue examined, as well as detailed skeletal examinations, are needed in order to properly evaluate the teratogenic potential of this chemical.

III.CONCLUSIONS

Administration of Dazomet technical to pregnant female American Dutch rabbits resulted in maternal toxicity at 25, 50 and 75 mg/kg/day. There was evidence of developmental toxicity of dazomet at the dose levels tested, but insufficient evidence was presented to conclusively demonstrate developmental toxicity.

Maternal NOEL= 12.5 mg/kg/day
Maternal LOEL= 25 mg/kg/day (decreased body weight gain on days 0-20 [study #2]).

Tentative Developmental toxicity NOEL = 12.5 mg/kg/day
Tentative Developmental toxicity LEL = 25 mg/kg/day (increased resorptions and resorptions/dam)

IV. CLASSIFICATION Core supplementary

This study does not satisify the guideline requirements (83-3) for a teratogenicity study in rabbits and cannot be upgraded. The registrant is asked to repeat this study at appropriate dose levels using an adequate number of dams to produce at least 12 litters/dose group.

Dazomet

Page____ is not included in this copy.

Pages 139 through 143 are not included.

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 quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

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Reviewed by: Timothy F. McMahon, Ph.D. 10/7/91
Section I, Toxicology Branch II (H7509C)
Secondary Reviewer: Stephen C. Dapson, Ph.D. Stephen C. Dapson 10/16/91
Section I, Toxicology Branch II (H7509C)

Data Evaluation Report

Study type: Multigeneration Reproduction - Rat (Guideline 83-4)

EPA ID Numbers: MRID number: 418653-01
Caswell No: 840
HED Project No: 1-1900

Test material: Dazomet

Synonyms: tetrahydro-3,5-dimethyl-2 H-1,3,5-thiadiazene-2-thione

Study number(s): 71R0318/8597

Sponsor: BASF Corporation
Research Triangle Park, NC

Testing Facility: BASF Aktiengesellschaft
Department of Toxicology
W. Germany

Title of report: Report on the Reproduction Study with Dazomet in Rats; Continuous Dietary Administration Over 2 Generations (2 Litters in the First and 1 Litter in the Second Generation)

Author(s): Dr. Hellwig

Study Completed: February 1989

Conclusions: The reproductive toxicity of Dazomet was assessed in male and female Wistar rats by administration of dazomet over two-generations at doses of 0ppm, 5ppm, 30ppm, and 180ppm. Reduced body weight and body weight gain was observed in F_0 females, F1 males, and F1 females at the 30 and 180ppm dose level. Reduced body weight and body weight gain was also observed in nursing F1 female rats at the 180ppm dose level. Increased liver : body weight ratios were observed in F_0 male rats and F1 males and females. Reduced activity of alanine aminotransferase activity in male and female F_0 rats at the 180ppm dose level was observed, as was significantly

decreased serum albumin in F_0 female rats at the 180ppm dose level, and significant decreases in serum globulins in F_0 and F1 male rats at the 180ppm dose level. An increase in the incidence and severity of intracellular hepatic neutral lipids was observed in F_0 and F1 male rats. No significant effects of test article administration were observed on reproductive performance or viability and survivial in pups of the F1a, F1b, and F2 generations.

IV. Classification: Core minimum

This study satisfies the data requirements (83-4) for a reproductive toxicity study in rats. Tables 070 and 071 are requested from the registrant in order to complete the database.

Parental Toxicity NOEL = 5ppm

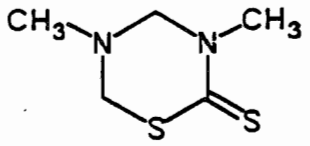
Parental Toxicity LEL = 30ppm (increased incidence and severity of hepatic intracellular neutral lipids in male rats; decreased body weight in F1 male rats)

Reproductive Toxicity NOEL = or > 180ppm

Reproductive Toxicity LEL- not achieved

I. MATERIALS AND METHODS

A. Test Material: Dazomet
purity: 98.2%; batch # 26-5297
description: not given in this study; described as a "white powder with a tinge of gray " in MRID# 418655-01.
structure:



B. Vehicle: dietary preparation

C. Test Animals: Species: Wistar rat (Chbb=THOM [SPF]), male and female
Source: Dr. Karl THOMAE, Biberach an der Riss, FRG.
Age: 28 days old at delivery; males and females from different litters in order to avoid sibling matings
Weight (mean): males, 138.3g; females, 122.5g at start of study. Range: males, 127-148g; females, 112-134g

D. Animal Husbandry

One hundred six male and 106 female Wistar rats were obtained for this study. Animals were allowed 8 days acclimation to the laboratory environment, during which rats with extreme body weight gain were eliminated and sacrificed. Ninety six male and female rats were actually used for this study, and the fate of the extra 10/sex was not stated, although it may be assumed that some of them were excluded due to extreme body weight. During the study period, rats were housed individually in type DK III stainless steel wire cages in a temperature (20-24 °C) and humidity (30-70%) controlled room with a 12 hour light/dark cycle. Food (Kliba rats/mice/hamsters maintenance diet "A" 343 meal) and municipal tap water were available ad libitum. The following exceptions were noted in the report (page 29):

1. During mating periods, males designated for this purpose were kept individually in Makrolon cages, type M III. Females were placed in cages with males for overnight mating. From day 18 of pregnancy until day 14 after birth, pregnent animals were also housed in Makrolon cages. Pregnant females were supplied with cellulose bedding toward the end of pregnancy.

E. Dietary Preparation and Analysis:

Dazomet was incorporated into ground diet at the required concentrations by weighing the required amount of test substance and mixing with a small amount of food in a beaker using a spatula. This premix was subsequently prepared in a BOSCH household mixer. Additional amounts of food were then added to the premix to obtain the desired final concentration, and mixing was carried out in a GEBR.LODIGE laboratory mixer for 10 minutes. Test diets were prepared twice a week and stored at 4 °C as soon as possible after mixing.

Stability of Dazomet in the diet was tested at room temperature, 4 °C, and at -20 °C. Results (page 1025 of the report) showed that dazomet was stable in the diet at room temperature for up to 2 days (as stated by the registrant; data for stability at 2 days not shown), and for 4 days at 4 °C.

Homogeneity of dazomet in dietary mixtures was examined at dietary concentrations of 5 mg/kg and 320 mg/kg. (page 1026 of the report). Although it was not specifically stated that samples for homogeneity analysis were taken from different parts of the batch diets, the results of this analysis (page 1026) indicate that the distribution of test material was homogenous at both doses tested.

In addition to the above, 2 samples of the test diet at each dose level used in the study were sent for analysis of test article concentration to the sponsor at the beginning of the study and at six-week intervals thereafter. Examination of the results of these analyses (pages 1028-1034) indicated that the concentration of test article was acceptable at each dose level for the duration of the study.

F. Procedures and Study Design

1) Mating:

Mating was initiated in the F_0 generation by placing the female in the cage of the male overnight . After each nocturnal mating, a vaginal smear was prepared from the female and investigated for the presence of sperm. If sperm was detected, the rat was considered to be fertilized. The maximum period of mating was 21 days. If no offspring were produced after the mating period, the partners were each mated with fertile animals of the control group in a 1:1 ratio. If one rat had not produced any offspring after the 2 matings (F1a and b litters) or after the mating for the F2 generation, those rats treated with test article were mated with fertile rats of the control group.

After successful mating, each pregnant female was individually placed into a cage with a solid bottom and bedding where they were allowed to litter and rear their pups until day 21 after parturition.

2) Mating schedule

Rats in the F_0 generation were administered test article continuously in the diet for 70 days prior to mating. Rats in the F_1 generation were mated in a ratio of 1:1 at least 98 days after their formation. Male partners were selected at random to avoid mating between siblings. Selection of parents for the F_1 generation was made after weaning of the F_1 generation.

3) Animal Assignment

F_0 rats were assigned to test groups using a randomization program according to body weight. Dose groups are summarized below:

Test groups	Dose (ppm) *	Animals per group ** Males	Females
1 Control	0	24	24
2 Low (LDT)	5	24	24
3 Mid	30	24	24
4 High (HDT)	180	24	24

*Diets were administered from the beginning of the study until the animals were sacrificed.

**The same number of animals were picked from the F1 litters as parents for the F2 generation.

G. Observation Schedule

1. Parental animals: Observations and the schedule for those observations is summarized from the report as follows:

Type of observation	Number of animals per sex per group	Frequency
Mortality and signs of toxicity	All	Once a day during premating and growth periods.
Detailed clinical observations	All	Once a day during growth and breeding periods.
Body weight	All	At beginning of study and weekly through growth and mating periods and again at necropsy.
Food consumption	All	Weekly during premating period and weekly from F1 generation formation until F1 mating.

(cont.)

Type of observation	Number of animals per sex per group	Frequency
Body weight	Maternal animals	Daily during mating periods (F1a and F1b litters); on days 0, 7, 14, and 20 of gestation; the day of parturition; and days 7, 14, and 21 post-partum.
Clinical chemistry	12 / sex / 0ppm and 180ppm dose groups	190 days after start of test article administration (Fo); 159 days after start of test article administration (F1).

2. Reproductive performance: Mating partners mating intervals, number of matings within an interval and time when positive sperm detection was made were noted. A mating was considered successful if evidence of sperm was found in vaginal smears.

The following indices were calculated:

$$\text{Fertility index} = \frac{\text{No. females pregnant}}{\text{Total no. females mated}} \times 100$$

$$\text{Gestation index} = \frac{\text{No. live litters born}}{\text{No. pregnancies}} \times 100$$

3. Litter observations: According to the report, the following litter observations were made:

Observation	Time of observation (lactation day) Birth	Day 4	Day 7	Day 14	Day 21
Number of live pups	checked daily				
Pup weight	x	x	x	x	x
External alterations	checked daily				
Number of dead pups	checked daily				
Sex of each pup	x				

Stillborn pups or pups that died during rearing were examined externally and organs eviscerated and examined microscopically. In addition to the above, the following behavioral tests on 3 male and 3 female pups/litter were performed in order to record any variations from normal:

-gripping (holding) reflex
-pupillary reflex
-hearing test

The following indices were calculated:

$$\text{Viability index} = \frac{\text{No. live pups at day 4}}{\text{No. pups born alive and stillborn at day 0}} \times 100$$

$$\text{Survival rate} = \frac{\text{no. live pups on day x after birth}}{\text{no. live pups at beginning of the day of birth (day 0)}} \times 100$$

$$\text{Lactation index} = \frac{\text{no. live pups on day 21 after birth}}{\text{no. live pups on day 4 after birth}} \times 100$$

4) Necropsy

a. Parental Animals: Animals of the F_0 generation were sacrificed following the weaning of the F1b pups. According to data supplied by the registrant (page 37 of the report), lactation of the F1b pups ended on November 30, 1986, and sacrifice of parental animals occurred on December 9, 1986. F_0 animals were subjected to post mortem examination as follows:

Animals examined	Macroscopic	Microscopic
Found dead	-	-
Unscheduled sacrifice	-	-
Scheduled sacrifice	x	x

Sections of the liver, testes, epididymides, prostate, coagulating glands, seminal vesicles, ovaries, uterus, vagina, pituitary gland, and all organs with macroscopic abnormalities were examined in rats from the control and high dose groups. Rats in the low and mid dose groups received

examination of the liver and all organs with macroscopic abnormalities.

b. Offspring: The F1, and F2 offspring were sacrificed at 21 days of age. These animals were subjected to post mortem examinations as follows:

Animals examined	Macroscopic	Microscopic
Found dead	x	
Scheduled sacrifice	x	

c. Necropsy observations: Gross necropsy consisted of external and internal examinations including the cervical, thoracic, and abdominal viscera.

The following tissues were prepared for microscopic examination:

X Ovaries	X Epididymides
X Uterus	X Prostate
X Unusual lesions	X Seminal vessicles
X Vagina/cervix	X Testes

Additional tissues prepared for microscopic examination included the liver, coagulating glands, and pituitary gland.

H. Data Analysis

1. Quantitative continuous random variables (e.g. body weight) were examined using trend analysis. Quantitative discrete random variables (e.g. , number of pups at the beginning of day 0 after birth) were analyzed using a linear rank test. Binomial frequencies (e.g. conception rate) were analyzed using Fisher's exact test for 2 x 2 contingency tables.

Clinical chemistry results were analyzed by analysis of variance and Dunnett's test Statistical evaluation of body weights and absolute and relative organ weight was performed using Dunnett's test.

II. REPORTED RESULTS

A. Parental Animals

1. Mortality and clinical signs: No mortality was observed in either F_0 or F1 parental rats during the study period. There were no overt clinical signs which appeared related to test article treatment in either the F_0 or F1 male and female rats. Results of blood chemistry measurements in F_0 and F1

rats are summarized below:

Observation and study week	Dose group 0 ppm males	0 ppm females	180 ppm males	180 ppm females
F_0 parental rats				
alanine aminotransferase (µkat/l)	1.18±0.29	0.86±0.10	0.94±0.13*	0.70±0.08**
albumin (g/l)	36.67±1.28	36.78±2.37	36.95±1.87	34.38±2.30*
globulin (g/l)	32.09±2.27	28.06±3.69	29.84±1.75*	28.39±1.63
F1 parental rats				
globulin (g/l)	29.21±2.99	27.17±1.45	26.34±2.77*	26.18±3.02

*significantly different vs control, $p < 0.05$
**significantly different vs control, $p < 0.01$

As shown, serum alanine aminotransferase was significantly decreased in both male and female rats in the 180ppm dose group of the F_0 generation. Albumin was signficantly decreased in F_0 female rats in the 180ppm dose group, while serum globulin was significantly decreased in male rats of the F_0 and F1 generation at 180ppm. There were no apparent effects of test article administration on serum activity of aspartate aminotransferase or alkaline phosphatase in either F_0 or F1 rats.

2. Body weight and food consumption:

Reported body weight (mean ± S.D.) and selected food consumption (mean ±S.D. results are summarized as follows:

F0 Generation Males - Pre-mating

Observation and study week	Dose group 0 ppm	5 ppm	30 ppm	180 ppm
Mean body weight (g)				
week 0	138.2±4.9	137.8±5.3	139.3±5.2	137.8±5.0
week 10	402.2±28.3	395.9±30.6	396.6±26.8	389.1±24.5
Mean weight gain (g)				
weeks 0 - 10	264	258.1	257.3	251.3
Mean food consumption (g/rat/day)				
week 1	21.9±2.0	22.3±1.7	22.4±1.6	21.4±1.8
week 2	24.2±1.8	23.7±2.4	25.2±1.8	24.8±1.6
week 10	28.0±2.6	27.1±3.1	27.6±3.2	27.1±3.0

F0 Generation Females - Pre-mating

Mean body weight (g)				
week 0	122.6±4.9	122.6±5.2	122.8±5.0	121.9±5.2
week10	242.8±18.6	242.1±15.9	242.8±21.5	234±17.9
Mean weight gain (g)				
weeks 0 - 10	120.2	119.5	120	112.1
Mean food consumption (g/rat/day)				
week 1	18.8±1.6	19.4±2.7	19.0±1.3	18.5±1.7
week 5	20.7±2.7	20.7±3.1	21.5±3.3	19.9±3.0
week 6	21.0±3.0	22.1±2.5	21.5±2.4	21.5±2.7

(cont.)

Observation and study week	Dose group 0 ppm	5 ppm	30 ppm	180 ppm
week 7	20.8±2.9	22.3±2.4	21.1±3.0	21.0±2.2
week 8	19.8±2.8	20.3±2.8	20.8±2.4	19.7±2.7
week 10	20.5±2.5	21.2±2.1	21.1±2.0	20.5±1.9

* Statistically significantly different from control, $p<0.05$.
** Statistically significantly different from control, $p<0.01$.

F1 Generation Males - Pre-mating

Observation and study week	Dose group 0 ppm	5 ppm	30 ppm	180 ppm
Mean body weight (g)				
week 0	119.6±11.3	126.2±13.1	123.9±13.4	111.3±10.4*
week 10	420.8±29.3	416.1±33.4	401.1±25.7*	390.7±34.1**
Mean weight gain (g) weeks 0 - 10	301.2	289.9	277.2	279.4
Mean food consumption (g/rat/day)				
week 1	22.4±1.9	22.8±2.1	21.9±2.0	20.6±1.8
week 6	29.7±3.0	30.3±2.6	28.8±2.6	30.3±3.3
week 10	30.9±2.7	31.3±4.1	29.2±2.9	30.4±3.6

F1 Generation Females - Pre-mating

Observation and study week	Dose group 0 ppm	5 ppm	30 ppm	180 ppm
Mean body weight (g)				
week 0	109.6±10.3	110.9±10.9	113.4±12.9	99.4±8.2**
week 10	254.4±17.7	253.7±21.1	257.8±19.4	243.5±22.1
Mean weight gain (g)				
week 0 - 10	144.8	142.8	144.4	144.1
Mean food consumption (g/rat/day)				
week 1	19.9±1.5	20.0±1.8	20.2±2.1	18.1±1.4
week 4	21.7±2.7	21.3±1.7	21.9±2.1	21.6±1.8
week 8	22.0±2.2	21.5±2.0	22.4±2.5	21.3±2.4
week 10	23.4±4.3	22.3±3.7	22.7±3.5	21.7±1.7

* Statistically significantly different from control, $p<0.05$.
** Statistically significantly different from control, $p<0.01$.

Selected group mean body weights and food consumption values for pregnant or nursing dams are summarized as follows:

F0 Generation - Litter A

Observation and study week	Dose group 0 ppm	5 ppm	30 ppm	180 ppm
Mean body weight (g)				
Day 0 of gestation	245.3±18.8	245.4±15.9	244.1±20.4	238.3±18.3
Day 20 of gestation	357.2±25.9	361.1±33.2	355.4 ±37.0	343.6±24.8

(cont.)

Observation and study week	Dose group 0 ppm	5 ppm	30 ppm	180 ppm
Mean body weight (g)				
Day 0 of lactation	277±20.1	282.8±18.9	276.4±20.2	269.1±20.8
Day 21 of lactation	304.6±19.6	306.2±18.2	300.4±24.3	287.0±20.4**
Mean body weight gain (g)				
Days 0-20 of gestation	111.9	115.7	111.3	105.3
Day 0-21 of lactation	27.6	23.4	24.0	17.9

F0 Generation - Litter B

Observation and study week	Dose group 0 ppm	5 ppm	30 ppm	180 ppm
Mean body weight (g)				
Day 0 of gestation	282.9±21.0	287.2±19.7	287.4±20.3	270.0±21.3*
Day 20 of gestation	408.0±40.2	417.5±27.0	405.5±52.5	382.3±39.8*
Day 0 of lactation	316.8±20.6	324.9±26.1	326.0±23.7	302.6±24.4
Day 21 of lactation	323.6±22.6	331.8±26.1	330.5±27.2	310.3±25.2
Mean body weight gain (g)				
Days 1-22 of gestation	125.1	130.3	118.1	112.3
Day 1-29 of lactation	6.8	6.9	4.5	7.7

F1 Generation

Observation and study week	Dose group 0 ppm	5 ppm	30 ppm	180 ppm
Mean body weight (g)				
Day 0 of gestation	270.4±18.9	270.6±22.2	275.2±17.9	259.8±20.3
Day 20 of gestation	393.6±26.9	387.4±30.9	404.5±32.2	368.2±36.9**
Day 0 of lactation	309.2±22.3	304.0±25.8	312.7±24.9	293.4±24.1*
Day 21 of lactation	324.2±18.9	325.0±26.3	328.8±18.6	301.0±23.6**
Mean body weight gain (g)				
Days 0-20 of gestation	123.2	116.8	129.3	108.4
Day 0-21 of lactation	15.0	21.0	16.1	7.6

* Statistically significantly different from control, $p<0.05$.
** Statistically significantly different from control, $p<0.01$.

3. Test Substance Intake

Intake of test material was calculated from the amount of feed consumed according to the following formula:

$$\frac{FC * D}{BW_X} = \text{test substance intake in mg/kg/day}$$

FC = mean daily food consumption in grams

D = dose in ppm

BW_X = mean body weight (in grams) on a specific day

Values listed in the report were derived from the daily intakes of test substance by individual animals. Test substance intake (in mg/kg/day) for the pre-mating period in F_0 (days 0-76) and F1 (days 0-104) parental rats is summarized below:

F_o Generation

Observation	Dose group 0 ppm	5 ppm	30 ppm	180 ppm
Test article intake (mg/kg/day)				
Males	0.0±0.0	0.46±0.2	2.78±0.13	16.98±0.7
Females	0.0±0.0	0.54±0.04	3.19±0.16	19.0±1.0

F1 Generation

Observation	Dose group 0 ppm	5 ppm	30 ppm	180 ppm
Test article intake (mg/kg/day)				
Males	0.0±0.0	0.46±0.03	2.71±0.09	17.06±0.85
Females	0.0±0.0	0.51±0.03	3.11±0.2	18.92±0.94

4. Reproductive performance

According to the registrant (page 39 of the report) there were no treatment-related effects on reproductive performance in the F_o generation.

Results for the parental animals are summarized from the report as follows:

F0 Generation - Litter A

Observation	Dose group 0 ppm	5 ppm	30 ppm	180 ppm
Median precoital interval (days)	1	1	1	1

(cont.)

Observation	Dose group 0 ppm	5 ppm	30 ppm	180 ppm
Males				
Mated	24	24	24	24
Fertile	24	24	24	24[a]
Fertility not determined	0	0	0	0
Intercurrent deaths	0	0	0	0
Females				
Number mated	24	24	24	24
Number fertile	24	24	24[a]	24
Fertility not determined	0	0	0	0
Intercurrent deaths	0	0	0	0
Mean gestation interval (days)	22.1	22.0	22.2	22.2
Number of litters	24.0	23.0	21.0	23.0
Total litter losses (no. rats)	6.0	5.0	4.0	4.0
Mean litter size (Day 0)	13.0	12.7	13.6	12.3
Mean litter size (Day 21)	12.2	12.3	13.0	11.8
Number of pups (Day 0)	313.0	294.0	286.0	284.0
Number of pups (Day 21)	294.0	284.0	274.0	273.0
Pup deaths (Days 0-21)	19.0	10.0	12.0	11.0
Mean pup weight (g) (Day 0; M+ F)	5.72	5.93	6.04	5.76
Mean pup weight (g) (Day 21; M+F)	43.9	46.8	46.2	43.9

*Statistically significantly different from control, $p<0.05$.
**Statistically significantly different from control, $p<0.01$.
[a]one rat in the 180ppm dose group was re-evaluated for fertility and found to be fertile.

F0 Generation - Litter B

Observation	Dose group 0 ppm	5 ppm	30 ppm	180 ppm
Median precoital interval (days)	2	2	2	2
Males				
Mated	ND	24	ND	ND
Fertile	ND	24	ND	ND
Fertility not determined	ND	0	ND	ND
Intercurrent deaths	ND	0	ND	ND
Females				
Number mated	ND	24	ND	ND
Number fertile	ND	24	ND	ND
Fertility not determined	ND	0	ND	ND
Intercurrent deaths	ND	0	ND	ND
Median gestation interval (days)	22.1	22.0	22.0	22.0
Number of litters (Day 0)	23.0	24.0	20.0	22.0
Total litter losses (no. rats)	4.0	6.0	11.0	1.0
Mean litter size (Day 0)	14.1	13.8	14.8	13.0
Mean litter size (Day 21)	13.7	13.2	14.0	12.6
Number of pups (Day 0)	326.0	333.0	296.0	287.0
Number of pups (Day 21)	316.0	319.0	280.0	279.0
Pup deaths (Days 1-29)	10.0	14.0	16.0	8.0
Mean pup weight (g) (Day 0; M+F)	5.92	5.90	5.96	5.81
Mean pup weight (g) (Day 21)	41.1	43.6	42.7	41.0

(cont.)

* Statistically significantly different from control, p<0.05.
** Statistically significantly different from control, p<0.01.
ND, no data available to determine these parameters (Tables 070 and 071 missing).

F1 Generation

Observation	Dose group 0 ppm	5 ppm	30 ppm	180 ppm
Median precoital interval (days)	1	1	1	1
Males				
Mated	24	24	24	24
Fertile	24	24	24	22[a]
Fertility not determined	0	0	0	0
Intercurrent deaths	0	0	0	0
Females				
Number mated	24	24	24	24
Number fertile	24	24	24	22
Fertility not determined	0	0	0	0
Intercurrent deaths	0	0	0	0
Median gestation interval (days)	22.2	22.5	22.2	22.2
Number of litters (Day 0)	24.0	24.0	24.0	22.0
Total litter losses (no. rats)	4.0	11.0	10.0	6.0
Mean litter size (Day 0)	13.2	12.9	13.6	13.2
Mean litter size (Day 21)	12.5	11.0	12.5	11.5
Number of pups (Day 0)	319.0	311.0	327.0	291.0
Number of pups (Day 21)	301.0	266.0	301.0	254.0
Pup deaths (Days 0-21)	18.0	45.0	26.0	37.0
Mean pup weight (g) (Day 0; M+F)	5.78	5.72	5.96	5.74
Mean pup weight (g) (Day 21; M+F)	42.9	45.4	45.5	41.6

* Statistically significantly different from control, p<0.05.
** Statistically significantly different from control, p<0.01.

5. Necropsy results

a. Organ weights: Liver weight results for male and female parental rats from the F_0 and F1 generation are summarized from the report (page 1044) as follows:

F0 Generation

Observation	Dose group 0 ppm	5 ppm	30 ppm	180 ppm
Males				
Liver weight (g)	14.6±1.48	13.8±1.68	14.0±1.60	15.0±1.76
Liver:body weight ratio (%)	2.98±0.2	2.87±0.17	2.93±0.19	3.15±0.18**
Females				
Liver weight (g)	9.30±0.8	9.4±0.8	9.16±1.0	9.15±0.9
Liver:body weight ratio (%)	3.28±0.23	3.25±0.14	3.21±0.26	3.44±0.36

F1 Generation

Males				
Liver weight (g)	15.8±2.15	15.9±2.70	15.9±2.74	15.9±2.7
Liver:body weight ratio (%)	3.22±0.3	3.24±0.37	3.40±0.46	3.54±0.44*
Females				
Liver weight (g)	10.5±1.42	10.5±1.42	11.2±0.99	11.4±1.14
Liver: body weight ratio (%)	3.74±0.37	3.70±0.44	3.91±0.29	4.38±0.48**

* Statistically significantly different from control, $p<0.05$.
** Statistically significantly different from control, $p<0.01$.

b. Pathology

i. Macroscopic examination

There were no treatment-related macroscopic findings noted in either male or female rats from the F_0 or F1 generation.

ii. Microscopic examination

As noted in the report (page 1042), the incidence and severity of fatty change was higher in treated rats than control in both the F_0 and F1 generation. This lesion was apparent in male but not female rats. Summary of this lesion for male rats is made below:

F0 Generation

Observation	Dose group 0 ppm	5 ppm	30 ppm	180 ppm
Number Examined	24	24	24	24
Liver-fatty change- incidence	4	4	7	20

F1 Generation

Observation	Dose group 0 ppm	5 ppm	30 ppm	180 ppm
Number Examined	24	24	24	24
Liver-fatty change- incidence	3	6	10	13

In addition to the apparent dose-related increase in the incidence of fatty liver, the severity of this lesion was also increased with dose. As shown on page 1093 and 1094 of the report, the severity of this pathologic change was graded as either minimal or slight in rats from the control, 5ppm, and 30ppm dose grouips from both the F_0 and F1 generations. In the 180ppm dose group of the F_0 generation, however, 4 of 20 rats were graded as moderate, while 2 of 20 were graded as severe. In the F1 generation, 1 rat each was graded as moderate and severe. Thus, the incidence and severity of this microscopic change in the liver was apparently related to test article treatment.

C. Offspring

1. Viability and clinical signs:

The registrant stated (page 64 of the report) that there were no clinical symptoms related to administration of test article. Only slight spontaneous findings were noted in a few individual pups of all groups, including control. Spontaneous findings occurred to a similar extent in F1a and F1b pups.

Viability results from pups during lactation are summarized from the report (beginning on page 652) as follows:

F1 Generation

Observation	Dose group 0 ppm	5 ppm	30 ppm	180 ppm
Litter A				
Mean percentage surviving in each litter (day 21)	93	96	95	96
No. litters with all pups surviving to Day 21/total no. litters	16/24(66%)	14/23 (60%)	13/21(61%)	13/23 (56%)
Litter B				
Mean percentage surviving in each litter (day 21)	96	95	94	97
No. litters with all pups surviving to Day 21/total no. litters	19/23 (82%)	16/24 (66%)	13/21 (61%)	15/22(68%)

F2 Generation (page 940 of report)

Mean percentage surviving in each litter (day 21)	94	85	92	87
No. litters with all pups surviving to Day 21/total no. litters	13/24 (54%)	12/24 (50%)	10/24 (41%)	10/22 (45%

* Statistically significantly different from control, $p<0.05$.
** Statistically significantly different from control, $p<0.01$.

Changes in mean litter sizes were summarized in the report (page 208) as follows:

F1 Generation

Observation and study time	Dose group 0 ppm	5 ppm	30 ppm	180 ppm
Litter A				
Day 1	12.29	12.39	13.24	11.96
Day 5	12.25	12.39	13.05	11.91
Day 11	12.25	12.35	13.05	11.91
Day 21	12.25	12.35	13.05	11.87

(cont.)

Observation and study time	Dose group 0 ppm	5 ppm	30 ppm	180 ppm
Litter B				
Day 1	13.87	13.42	14.05	12.91
Day 5	13.83	13.33	14.00	12.82
Day 11	13.78	13.29	14.00	12.82
Day 21	13.74	13.29	14.00	12.68
	F2 Generation (page 314)			
Day 1	12.75	12.00	12.88	12.23
Day 5	12.58	11.13	12.58	11.64
Day 11	12.54	11.08	12.54	11.55
Day 21	12.54	11.08	12.54	11.55

* Statistically significantly different from control, $p<0.05$.
** Statistically significantly different from control, $p<0.01$.

The registrant stated (page 64 of the report) that there were no clinical symptoms in F1a or F1b pups related to administration of test article. Slight, spontaneous findings such as alopecia, blood crusted around the eyes, and hematoma, were found in a few individual pups of all dose groups, including control.

2. Body weight:
Selected group mean body weights are summarized from the report as follows:

F1 Generation

Observation and study time	Dose group 0 ppm	5 ppm	30 ppm	180 ppm
Litter A				
Males				
Body weight (g) - Day 0	5.89±0.51	6.09±0.56	6.22±0.47	5.93±0.37
Weight gain (g) - Days 0-21	38.79±5.9	41.85±5.8	41.03±6.0	38.88±5.0
Females				
Body weight (g) - Day 0	5.55±0.47	5.77±0.38	5.86±0.51	5.60±0.45
Weight gain (g) - Days 0-21	37.69±5.1	39.93±5.1	39.38±6.3	37.5±5.0

(cont.)

Observation and study time	Dose group 0 ppm	5 ppm	30 ppm	180 ppm
Litter B				
Males				
Body weight (g) - Day 0	6.06±0.47	6.05±0.50	6.12±0.33	5.99±0.32
Weight gain (g) - Days 0-21	35.84±7.8	38.46±8.4	37.24±5.3	35.82±6.0
Females				
Body weight (g) - Day 0	5.79±0.42	5.76±0.40	5.81±0.25	5.64±0.34
Weight gain (g) - Days 0-21	34.57±7.01	36.98±7.9	36.40±5.0	34.60±6.0
F2 Generation				
Males				
Body weight (g) - Day 0	6.02±0.48	5.89±0.39	6.14±0.56	5.89±0.52
Weight gain (g) - Days 0-21	37.99±5.8	40.97±7.4	40.61±6.4	36.90±5.9
Females				
Body weight (g) - Day 0	5.55±0.33	5.56±0.37	5.79±0.50	5.60±0.52
Weight gain (g) - Days 0-21	36.25±4.9	38.58±6.8	38.64±5.6	34.80±4.4

* Statistically significantly different from control, $p<0.05$.
** Statistically significantly different from control, $p<0.01$.

3. Necropsy results

a. Organ weights:

Organ weights were not apparently recorded in pups from the F1 or F2 generation.

b. Pathology

i. Macroscopic examination:

According to the registrant (pages 67 and 77, gross examination of pups from the F1 and F2 generations did not reveal any differences between test groups in either the type or number of

malformations, variations, and/or retardations.

The registrant stated (page 35) that with the exception of the F1a pups used as the basis of the F1 parental generation, all pups, *including* stillborn pups and those that died during their rearing period, were subjected to a macroscopic examination. However, the report lists macroscopic findings only for those pups stillborn, pups that died intercurrently, or surplus pups. Thus the fate of the remaining pups is not known.

c. Developmental Stages and Behavioral Tests

Erection of the auricles (day 4 after birth), opening of the auditory canal (day 13 after birth), and opening of the eyes (day 16 after birth) was monitored in F1 and F2 pups, as well as the previously mentioned behavioral tests.

Examination of the results of these tests (pages 172-207 of the report) showed that there were no differences in developmental stages or behavioral performance among pups of the control and treated groups in the F1 and F2 generations.

III. DISCUSSION

A. Investigators' conclusions

The conclusions of the registrant are appended to this review.

B. Reviewer's discussion

In the present study, the reproductive toxicity of dazomet was assessed in male and female Wistar rats. Groups of 24 male and female rats selected as the F_0 generation were given dazomet in the diet at levels of 0ppm, 5ppm, 30ppm, and 180ppm. After 70 days of treatment, F_0 rats were mated to produce the F1a litter and then mated again following weaning of the F1a litter to produce the F1b litter. Groups of 24 male and 24 female rats were selected from the F1a litter as F1 parents and administered dazomet in the diet post-weaning at 0, 5, 30, and 180ppm until weaning of the F2 litter, at which time the study was terminated. The following parameters were measured in both F_0 and F1 generations parents: body weight and body weight gain (once weekly until necropsy); food consumption (once weekly, except during pregnancy and lactation of the dams, when food consumption was determined on working days); clinical symptoms (once daily); mating performance; mortality (once daily check); macroscopic and microscopic examination at necropsy; blood chemistry measurements at 190 days after start of treatment (F_0 parents) and 159 days after the start of treatment (F1 parents).

Toxicity in F_0 parental rats was evident mainly at the 180ppm dose level. At this dose, decreased body weight gain (7%) was noted in F_0 female rats for the first 10 weeks of the study (112g weight gain vs 120g weight gain in controls). Body weight and body weight gain were not apparently

affected to a significant degree in F_0 male rats.

In F1 parental rats, decreased body weight was observed in male rats at the 180ppm dose group at the start of dosing (111g vs 119g in controls). At week 10 of test article administration in F1 male rats, significantly reduced body weight was observed in the 30ppm and 180ppm dose groups of F1 male rats vs controls (decreases of 5% and 8%, respectively, $p < 0.05$). Mean food consumption was not affected during this period, supporting the conclusion of test article-related toxicity. Female rats in the F1 parental generation were also observed with decreased absolute body weight at the start of test article administration (99g vs 109g). However, body weight gain and food consumption in female F1 rats was unaffected from weeks 1-10.

In nursing dams, body weight gain during lactation was decreased in all dose groups vs control in the F_0 litter A generation by at least 13%, while body weight gain in the F_0 litter B generation was decreased by 11% in the 180ppm dose group during gestation , but not during lactation. In F1 nursing females, body weight was decreased significantly in the 180ppm dose group on day 0 and day 21 of lactation, and significantly decreased body weight gain was also observed in the 180ppm dose group from days 0-29 of lactation (decrease of 12%, $p < 0.05$). Body weight gain in F1 females was decreased by 50% vs control at the 180ppm dose level during lactation.

Changes in absolute and relative liver weight were found in the F_0 and F1 parental generations. These effects occurred primarily at the 180ppm dose level, and included significantly increased liver : body weight ratio in F_0 male rats ($p < 0.01$) and F1 male and female rats. Apparently, the increased liver:body weight ratio observed in these groups was the result of an effect on body weight, as the absolute liver weight in F_0 males and F1 males and females at the 180ppm dose level was not significantly altered from controls.

While no abnormalities in macroscopic pathology were reported in F_0 or F1 parental rats, increased incidence and severity of intracellular neutral lipids was observed as an abnormality upon microscopic examination of the liver in F_0 and F1 male rats. The incidence and severity of this lesion was increased with dose, primarily in male rats, establishing this effect as test article related.

Clinical chemistry observations in F_0 and F1 parental rats included significantly decreased alanine aminotransferase activity in male and female F_0 rats at the 180ppm dose level, significantly decreased serum albumin in F_0 female rats at the 180ppm dose level, and significant decreases in serum globulins in F_0 and F1 male rats at the 180ppm dose level. The phenomenon of decreased serum albumin and globulins has also been observed in a subchronic toxicity study in rats (MRID # 418655-02), and supports the conclusion of a test article-related effect on blood protein, although the mechanism of this effect is not known.

In contrast to effects observed on parental rats in this study, there was no apparent effect of dazomet administration on reproductive performance, although Tables 070 and 071, which list fertility status of the F1b parental rats, was missing. Gestation and lactation indices were unaffected by test article treatment in the F1a, F1b, and F2 pups. Survival and viability of the pups was also unaffected, with the exception of survival of the F1b pups, where the percentage of litters with all pups surviving to day 22 was decreased from control (66%, 61%, and 68% in the 5ppm, 30ppm, and 180ppm dose groups vs 82% in control, respectively). There were no other reported effects of test article in either the F1a, F1b, or F2 pups in this study.

IV. CLASSIFICATION: Core minimum

This study satisfies the data requirements (83-4) for a reproductive toxicity study in rats. Tables 070 and 071 are requested from the registrant in order to complete the database.

Parental Toxicity NOEL = 5ppm

Parental Toxicity LEL = 30ppm (increased incidence and severity of hepatic intracellular neutral lipids in male rats; decreased body weight in F1 male rats)

Reproductive Toxicity NOEL = or > 180ppm

Reproductive Toxicity LEL- not achieved

Dazomet

Page_____ is not included in this copy.

Pages 170 through 171 are not included.

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 quality control procedures.

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