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

008315

APR - 1

PENDING REGISTRATION INFORMATION IS NOT INCLUDED

OFFICE OF PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Expedited Review re: SAN 582H/Experimental Use Permit

Caswell No. 195J HED Project No. 0-1832

TO: Sangeeta Vohra
Product Team 23
Registration Division (H7505C)

FROM: Deborah L. McCall DLMcCall 3-27-91
Section III/ HFAS / HED / Toxicology Branch II / (H7509C)

THROUGH: James Rowe, Ph.D., Section Head James N. Rowe 3/27/91
Section III / HFAS / HED / Toxicology Branch II / (H7509C)
and
Marcia Van Gemert, Ph.D., Branch Chief Marcia Gemert 3/28/91
HFAS / HED / Toxicology Branch II / (H7509C)
and
William Burnam, Deputy Director W. Burnam 3/29/91
Health Effects Division (H7509C)

BACKGROUND: The registrant (Sandoz Crop Protection Corporation) has submitted 21 studies in support of an Experimental Use Permit for [redacted] and a tolerance petition for corn (0.1 ppm). These studies have been evaluated, and summaries of the studies are attached (Appendix I). [redacted] However, concerning the "G" Petition - temporary tolerance for Corn (0.1 ppm), the TOX II branch had possible carcinogenicity concerns due to positive mutagenicity data. It was requested that chronic data be submitted to address the cancer concerns.

ACTION: A two-year chronic/carcinogenicity bioassay in rats and a mouse carcinogenicity bioassay were under review and nearly completed at the same time the EUP was under consideration. Therefore, it was requested by Product Team 23 (S. Vohra) that an expedited review of the two bioassays be completed, if possible, in order to resolve the issue of the positive mutagenicity findings. Conclusions from the reviews are presented below (and the DERs are attached):

1) Mouse Carcinogenicity (§83-2); MRID No. 416624-15

SAN 582H was administered to Crl:CD-1 (ICR) BR mice of both sexes for a period of 94 weeks in the diet at dose levels of 0, 30, 300, 1500 or 3000 ppm. SAN 582H did not affect the distribution or rate of mortality.

Significantly decreased ($p<0.01$) body weight gains were observed at 3000 ppm for males during the first 26 weeks of treatment, and for females during weeks 26-52 of treatment. For both sexes, the decrease in body weight gains was not statistically significant for the overall 0-94 week period.

Terminal sacrifice non-neoplastic histopathology indicated that there was a dose-related generalized hepatocyte enlargement (minimal) in treated animals of both sexes. Likewise, interim sacrifice non-neoplastic histopathology indicated an increase in centrilobular hepatocyte enlargement in high-dose animals of both sexes. In addition, at interim sacrifice non-neoplastic histopathology revealed minimal hyperkeratosis at the limiting ridge of the stomach in both sexes at 3000 ppm. This latter finding, was attributed to irritation and was not seen at terminal sacrifice.

Interim and terminal neoplastic histopathology did not reveal treatment-related effects on the incidence of tumor types or of mice with benign or malignant tumors. It is concluded that SAN 582H is not oncogenic in Crl:CD-1 (ICR) BR mice under the conditions of this bioassay.

Based on decreased body weight gains observed in both sexes during the first year of the study and in gross and histological observations enumerated in the discussion section of the attached DER, it is concluded that an MTD was achieved in this study.

This study meets the data requirements for a mouse carcinogenicity study (§83-2) and is classified as CORE MINIMUM.

2) Combined chronic toxicity/carcinogenicity study in rats (§83-5); MRID No. 417068-08

Technical SAN 582H was administered to male and female rats in the diet for 104 weeks at doses of 0, 100, 700, 1500 ppm. In males, benign tumors of the liver were observed at the 700 and 1500 ppm dose levels, with an incidence of 2% and 6% in these dose groups compared to 0% in controls. In female rats, benign tubular adenomas of the ovary were observed at an incidence of 12% in the 1500 ppm dose group vs 4% in controls. The incidence of non-neoplastic alterations in the liver, parathyroid, and stomach of males and the ovary of females was also increased by treatment with test article at 700 and 1500 ppm. The NOEL and LOEL were 100 and 700 ppm, respectively.

Based on the effect of test article on body weight, body weight gain, and histopathology it appears that the 1500 ppm dose level was the MTD in this study.

The data in this study support the conclusion of limited evidence of carcinogenicity for SAN 582H technical, based upon the occurrence of increased incidence of benign and malignant liver tumors only in high dose (1500 ppm) male rats, and the increased incidence of tubular

adenomas in female rats treated at 700 and 1500 ppm.

This study does not satisfy the guideline requirements (83-5) for a combined chronic/carcinogenicity study in rats and is classified as CORE SUPPLEMENTARY. The following information is requested in order to upgrade this study to core minimum:

1) The registrant is asked to provide recent historical control data on relevant tumor incidence from animals given the same type of diet as that used in the present study, or detailed composition of the diets used in both the historical control studies and the present study.

RECOMMENDATIONS:

It is doubtful that the issue of the potential carcinogenicity of SAN 582H in rats can be addressed by the HED RfD/Peer Review Committee by April 15th, the date for which the EUP [temporary tolerance for corn (0.1 ppm)] was requested. However, TOX II recommends that the registrant be allowed to apply SAN 582H to corn with the stipulations that 1) the applicators be adequately protected, 2) the crop should be destroyed and 3) there are no objections from other OPP disciplines.

APPENDIX I

SAN 582H TECHNICAL:

1) Acute Oral in Rats (§81-1) (MRID No. 416624-09) - The study was classified Guideline. LD50 = 2139.8 mg/kg in males and 1296.8 mg/kg in female rats. The combined LD50 = 1569.8 mg/kg. Toxicity Category III.

2) Acute Dermal in Rats (§81-2) (MRID No. 416624-10) - The study was classified as Guideline. LD50 > 2.0 mg/kg in both sexes. Toxicity Category III.

3) Acute Inhalation in Rats (§81-3) (MRID No. 416624-11) - The study was classified as Minimum. LC50 > 4990 mg/m^3 in male and female rats. Toxicity Category III.

4) Primary Eye Irritation in Rabbits (§81-4) (MRID No. 416624-12) - The study was classified as Minimum. Minimally irritating to the eyes of white rabbits. Toxicity Category III.

5) Primary Dermal Irritation in Rabbits (§81-5) (MRID No. 416624-13) -The study was classified as Guideline. Minimally irritating to the skin of male rabbits. Toxicity Category IV.

6) Dermal Sensitization in Guinea Pigs (§81-6) (MRID No. 417068-07) - The study was classified as Minimum. SAN 582H is a mild skin sensitizer in male guinea pigs.

7) 13-Week Oral Feeding Study in Rats (§82-1) (MRID No. 416159-01) - The study was classified as Minimum. The oral NOEL = 500 ppm and the LOEL = 1500 ppm. Compound related reductions in body weight, increase in relative liver weight, centrilobular hepatocytic enlargement and an increase in protein and cholesterol levels were observed at 1500 ppm or higher dose levels.

8) 13-Week Oral Feeding Study in Dogs (§82-1)(MRID No. 416159-02) - The study was classified as Minimum. NOEL = 100 ppm and the LOEL = 750 ppm. Periportal hepatocellular vacuolation was noted in the 2000 ppm (HDT) dose group. Histological liver changes were noted in the 750 and 2000 ppm dose group. Body weight and body weight gains of the 750 ppm (females only) and the 2000 ppm (males only) were depressed throughout the study.

9) 52-Week Oral Toxicity Study in Dogs (§83-1) (MRID No. 416159-03) - The study was classified as Guideline. NOEL = 250 ppm and the LOEL = 1250 ppm. Periportal hepatocyte vacuolation was noted in the 1250 ppm dose group. Liver changes in the 1250 ppm dose group correlates with the increase in serum alkaline phosphatase, cholesterol levels, and the increase in liver-to-body weight ratio.

10) Developmental study in Rats (§83-3) (MRID No. 416159-04) - The study was classified as Minimum. Maternal NOEL = 50 mg/kg/d and the LOEL = 215 mg/kg/d. Maternal toxicity was evidenced by excess salivation, increased liver weights and reduced body weight gain and food consumption in the 215 and 425 mg/kg (HDT). Developmental toxicity was evidenced by increased incidence of resorptions in the 425 mg/kg dose group. Developmental NOEL = 215 mg/kg/d and the LOEL = 425 mg/kg/d.

11) Two Generation Reproduction in Rats (§83-4) (MRID No. 416159-05) - The study was classified as Minimum. Parental toxicity NOEL = 500 ppm and the LOEL = 2000 ppm. Parental toxicity was evidenced by significant reductions in body weight and food consumption in males and significant increase in absolute and relative liver weights in both sexes of the 2000 ppm dose group. Significant reductions in pup weight during lactation were noted in the 2000 ppm dose group. The NOEL and LOEL for reproductive toxicity were 500 and 2000 ppm, respectively.

12) Salmonella/mammalian reverse activation gene mutation assay (§84-1) (MRID No. 415965-42) - The study was classified as Acceptable. No increase in mutant colonies of any strain at any dose either with or without S9 activation were noted.

13) In vitro Chromosome Aberration using Chinese hamster ovary (§84-2) (MRID No. 415965-43) - The study was classified as Unacceptable. Cytotoxicity was apparent at non-activated dose level of 125 to 150 µg/mL and S9-activated levels of 400 to 500 µg/mL. Study should be repeated at dose levels well below the cytotoxic dose.

14) Rat Primary Unscheduled DNA (in vitro) synthesis (§84-3)(MRID No. 415965-44) - The study was classified as Acceptable. Genotoxic (unequivocally positive), UDS activity occurred at levels well below the cytotoxic level.

15) Metabolism in Rats (§85-1) (MRID No. 415965-45) - The study was classified as Unacceptable. SAN 582H was extensively metabolized within 3 days after dosing. Less than 2.5% of the ^{14}C dose was recovered as unchanged parent compound, and 22 metabolites, 21 were found in the urine and feces and were identified. However, because 61 to 78% of the ^{14}C dose was not identified or characterized the study is unacceptable.

SAN 582H 7.5L:

1) Acute Oral Toxicity in Rats (§81-1) (MRID No. 415965-36) - The study was classified as Guideline. The LD50 = 2.4 g/kg for combined sexes. The male LD50 = 2.0 g/kg and the female LD50 = 2.8 g/kg. Clinical signs included: hypoactivity, clonic convulsions, tremors, ataxia, excess salivation, diarrhea, red-stained face and yellow-stained urogenital area. Toxicity Category III.

2) Acute Dermal Toxicity in Rabbits (§81-2) (MRID No. 415965-37) - The study was classified as Guideline. LD50 > 2.0 g/kg for combined sexes. No deaths occurred during the study. Clinical signs included: severe dermal irritation consisting of slight to severe erythema, atonia, and fissuring. No systemic toxicity was noted. Toxicity Category III.

3) Acute Inhalation Study in Rats (§81-3) (MRID No. 415965-38) - The study was classified as Minimum. LC50 > 3.39 mg/L. No deaths occurred during the study. Clinical signs included: partial closing of eyes, salivation, reduced respiratory rate and abnormal body position during exposure. After exposure the signs were: Ataxia, abnormal respiration, ocular discharge, and lethargy. Toxicity Category III.

4) Primary Eye Irritation in Rabbits (§81-4) (MRID No. 415965-39) - The study was classified as Guideline. Slight to severe conjunctival irritation, slight corneal opacity and iritis were observed up to day 7. All eyes were normal by day 21. Toxicity Category II.

5) Primary Dermal Irritation in Rabbits (§81-5) (MRID No. 415965-40) - The study was classified as Guideline. Primary Dermal Irritation score = 0.6, Slightly irritating. Slight to well-defined erythema was noted up to 72 hrs. and slight edema was noted up to 48 hrs. post exposure. No irritation was observed 96 hrs. post exposure. Toxicity Category IV.

6) Dermal Sensitization in Guinea Pigs (§81-6) (MRID No. 415965-41) - The study was classified as Guideline. SAN 582H is a dermal sensitizer, eliciting slight to moderate dermal reactions.

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Data Evaluation Report

Study type: Combined Chronic Toxicity/Carcinogenicity - rats
Guideline: 83-5

EPA ID Numbers: MRID number: 417068-08
Caswell No: 195J
HED Project No: 1-0405A

Test material: SAN 582H technical

Synonyms: 2-chloro-N-[(1-methyl-2-methoxy)ethyl]-N-(2,4-dimethyl-thien-3-yl) acetamide

Study number(s): SDZ 335/891445

Sponsor: Sandoz Crop Protection Corporation
Sandoz Ltd.
Agrochemical Toxicology Dept., Switzerland

Testing Facility: Huntingdon Research Centre Ltd.
Huntingdon, Cambridgeshire, England

Title of report: SAN 582H: Potential Tumorigenic and Toxic Effects in Prolonged Dietary Administration to Rats

Author(s): S.A. Ruckman, L.A. Waterson, D. Crook, D. Buist, W.A. Gibson, R. Read, C. Gopinath, A. Anderson, I.S. Dawe, D.O. Chanter.

Report Issued: March 1, 1990

Conclusions:

Technical SAN 582H was administered to male and female rats in the diet for 104 weeks at doses of 0, 100, 700, and 1500 ppm. In males, benign tumors of the liver were observed at the 700 and 1500 ppm dose levels, with an incidence of 2% and 6% in these dose groups compared to 0% in controls. In female rats, benign tubular adenomas of the ovary were observed at an incidence of 12% in the 1500 ppm dose group vs 4% in control. The incidence of non-neoplastic alterations in the liver, parathyroid, and stomach of males and the ovary of females was also increased by treatment with test article at 700 and 1500 ppm.

Based on the effect of test article on body weight, body weight gain, and histopathology it appears that the 1500 ppm dose level was the MTD in this study.

The data in this study support the conclusion of limited evidence of carcinogenicity for technical SAN 582H, based upon the occurrence of increased incidence of benign and malignant liver tumors only in high dose male rats, and the increased incidence of tubular adenomas in female rats treated at 700 and 1500 ppm SAN 582H.

The No Observed Effect Level (NOEL) = 100 ppm

The Lowest Observed Effect Level (LEL) = 700 ppm

The Maximum Tolerated Dose (MTD) = 1500 ppm (males and females)

Classification: Core Supplementary

This study does not satisfy the guideline requirements (83-5) for a combined carcinogenicity/ chronic toxicity study in rats. The following information is requested in order to upgrade this study to core minimum:

1) The registrant is asked to provide **recent** historical control data on relevant tumor incidence from animals given the same type of diet as that used in the present study, or detailed composition of the diets used in both the historical control studies and the present study.

I. MATERIALS AND METHODS

A. Test Material

SAN 582H; description: brown oil (batch # AD 8605); Purity (by pre-study analysis: 91.3%). Two batches of SAN 582H were received for use at Huntingdon Research Centre, one on November 28 1986, and the other on April 22, 1988 (page 20 of report). Days on which these two lots were used in the study were not given, nor was it stated whether the purity was equivalent between these two batches.

Test article was stated as stable until August 1990 by the sponsor. Stability of dietary formulations was assessed in a separate study by the performing laboratory (see below, and page 1339 of registrant report), and were found to be stable for up to 12 weeks in closed plastic bags.

B. Test Animals

Male and female Sprague-Dawley rats (cesarean derived, reared by cross-fostering); Source: Charles River Breeding Laboratories, Portage, Michigan, U.S.A. Age: approximately 28 days old upon receipt. Weight range (at time of dosing): males, 160-216g; females, 114-158g.

C. Dietary Mixtures

SAN 582H was administered by admixture with the diet in pellet form. Dietary pre-mixes were prepared approximately every month or every other month (based upon data provided by the performing laboratory, pages 1349-1358 of report) by incorporation of a weighed quantity of SAN 582H (dissolved in acetone) into untreated Rat and Mouse Maintenance Diet # 1. Acetone was driven off by rotary evaporation at 40 ^{o}C, and further quantities of untreated diet added until 2kg was attained. This admixture was then stirred thoroughly by hand.

The stirred 2kg pre-mix was added to untreated basal diet and mixed for a minimum of 7 minutes in a double cone rotary blender to obtain a 25kg pre-mix, which was then used for the pelleting procedure.

Pelleting procedures were according to standard practices of SDS Mills, Witham. The 25kg pre-mix was added to the blender with basal diet prior to pelleting to yield a final quantity of 250kg for pelleting. The finished product was packed in plastic inner bags with paper outer bags. The blender and pelleting press were cleaned prior to and following preparation of each batch of diets used in this study.

D. Stability and Homogeneity

Stability of dietary test mixtures was performed on trial diets prior to study initiation. Trial dietary mixtures of 50 and 3000 ppm were prepared and sampled for analysis prior to pelleting. Trial diets were sampled again immediately following the pelleting process for analysis, and the remaindor of each diet stored in feed hoppers under animal room conditions or in closed plastic bags under the same conditions for future analysis.

Representative samples from the trial diets stored in animal hoppers were analyzed after 2 weeks udner these storage conditions (Trial #1), while samples from the trial diets stored in plastic bags were analyzed at 1, 2, 4, 8, and 12 weeks (Trial #2). Results of this analysis (page 1346 of report) showed that concentrations of test article in powdered diet were within 5% of nominal, but that the pelleting process resulted in signifcant loss of test article, attributed to volatilization during the drying of pellets. Although loss of test article occurred upon drying of pellets, no significant change in dietary concentration of test article in pelleted diets occurred over time, demonstrating stability of test article in this dietary formulation. The loss of test article as a result of the pellet drying procedure was taken into account when making dose formulations.

Results of dose formulation analysis of test article concentration (pages 1349-1358) showed that the mean analyzed concentration of test article was within 15% of nominal at all dose levels, with the exception of one formulation of 100ppm, which was approximately 25% in excess of nominal, but which was replaced by a subsequent batch within acceptable limits.

Homogeneity of dietary test mixtures at each dose level was conducted in representative samples taken from points representing 60kg, 120kg, 180kg, and 240kg of each 250kg mix. Homogeneity of test article within the pellet was also assessed by analyzing the surface and core of pellet samples from the first dose formulation mixture. Results of these analyses (pages 1349-1358 of report) showed good homogeneity of test article diets at each dose

level, and homogeneity of test article within each pellet.

D. Animal Husbandry

A total of 688 rats (344 males and 344 females) were employed in this study. On arrival, rats were placed at random into suspended cages with wire mesh floors so that each cage contained 5 rats of the same sex. Five male and five female rats were selected at random, sacrificed, and examined macroscopically to determine the health status of the animals.

All rats had free access to food (SDS Rat and Mouse pelleted #1 modified maintenance diet) and tap water (in polypropylene bottles). Animals were housed in temperature (21 ± 1 ^{o}C) and humidity (50 ± 5%) controlled rooms, and permanent daily recordings were made of these parameters. A 12 hour light/dark cycle was employed.

Rats were acclimated to the animal room environment for 5 days. Following acclimation, each animal was weighed and selected or discarded based upon the deviation of body weight from 20% of the grand mean. Those animals selected were randomly assigned to cages in such a way that initial cage body weights were approximately equal. Cages were dispersed so that possible environmental influences arising from their distribution were equilibrated.

Prior to final assignment, rats were subjected to veterinary examination to ensure a healthy status. Following examination, a second acclimation period of 7 days was allowed before initiation of treatment.

E. Experimental Design and Dosing

Rats were assigned to one of four dose groups consisting of 50 males and 50 females in each group. These groups were used for evaluation of the tumorigenic potential of SAN 582H, and are as follows:

Group #	Dose Level (ppm)	No. of Rats male	female
1	0	50	50
2	100	50	50
3	700	50	50
4	1500	50	50

Four additional groups of 20 rats/sex/group were used for sampling of blood and interim sacrifice at 52 weeks.

Rats were housed within the same animal room for the entire course of the study, except

during weeks 4 and 5 of the study, when thay were apparently housed in an adjacent room, due to the "decoration" of the original animal room (page 22 of report).

SAN 582H was administered by dietary admixture in pellet form to all rats assigned to treatment groups. Control rats received diet treated with acetone and pelleted in the same way as the test diets.

E. Statistical Analysis

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

F. Compliance

A signed statement of no data confidentiality claims was provided.

A signed statement of GLP compliance was provided.

A signed statement of quality assurance was provided.

A signed statement of flagging studies for potential adverse effects was provided.

II. OBSERVATIONS AND RESULTS

A. **Health Check**

Of the rats selected at random for the pre-treatment health check, none were found with any changes considered to be related to infectious disease.

B. **Mortality**

Rats were observed early each morning and again in the afternoon for signs of mortality and/or moribundity. On weekends, the second observation time was made at midday. Any animal showing signs of debility or intoxication was killed by CO_2 asphyxiation and subjected to detailed macroscopic examination. Tissues were preserved in 10% buffered formalin where possible.

Cumulative mortality in male and female rats is summarized in the following Table (Table 1):

TABLE 1

Cumulative Mortality in Rats Given SAN 582H in the Diet for 104 Weeks [a]

Week of Study	Males				Females			
	0	100	700	1500	0	100	700	1500
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	1(2)	5(10)	2(4)	2(4)	0(0)	0(0)	0(0)	1(2)
78	11(22)	16(32)	7(14)	5(10)	9(18)	7(14)	4(8)	5(10)
104	32(64)	30(60)	25(50)	19(38)	25(50)	28(56)	20(40)	19(38)

[a]data calculated from pages 1382-1384 of registrant report.

[b]cumulative mortality (percent mortality)

No significant differences in mortality were observed between control and treated rats of either sex over the duration of treatment. There appeared to be a trend towards increased survival in rats of both sexes in the 700 and 1500 ppm dose groups, as shown by the decreased cumulative and percent mortality at 78 and 104 weeks for both sexes in these dose groups. Male and female rats in the 100 ppm dose group appeared to have a similar pattern of survival as control rats over the course of the study.

B. **Body Weights**

Rats were weighed at the time of assignment to the various treatment groups, on the first day of treatment, and then weekly thereafter during the course 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 SAN 582H in the Diet for 104 Weeks [a]

Week of Study	Males (g) 0	100	700	1500	Females (g) 0	100	700	1500
0	186	185	186	186	139	140	139	139
1	245	242	240	235	164	168	161	160
13	530	520	512	481	288	285	273	258
26	645	630	621	570	326	321	302	287
52	752	736	716	660	409	401	370	344
104	825	784	779	722	542	496	503	418

[a]data taken from Table 1a, pages 55-58 of registrant report.

Body weight in 700 and 1500ppm male rats as summarized by the registrant (page 59 of report) was significantly decreased in comparison to controls over weeks 1-10 of the study, and this trend was maintained over the duration of the study in this sex. Male rats in the 700 ppm dose group showed a decrease in body weight of between 4-6% during the first 13 weeks of the study beginning at week 4, while a decrease of approximately 10% was observed over the same time period in males in the 1500 ppm dose group. Thus, the effect of treatment on body weight appears dose related at 700 and 1500 ppm in male rats.

A similar phenomenon was observed in female rats in the 700 and 1500 ppm dose groups, but was slightly more pronounced ($p < 0.01$) for the duration of the study than in male rats ($p < 0.05$). The effect of test article at 700 and 1500 ppm on body weight in female rats also appeared dose-related.

Effects of test article treatment on body weight gain in male and female rats is summarized in the following Table (**Table** 3):

TABLE 3

Group Mean Body Weight Gains in Male and Female Rats Given SAN 582H in the Diet for 104 Weeks [a]

	Males				Females			
	0	100	700	1500	0	100	700	1500
Body weight (week 0)	186	185	186	186	139	140	139	139
Weight gain (grams):								
0-13	344	335	326	295	149	145	134	119
%control	-	97	94	85	-	97	90	80
0-52	566	551	530	474	270	261	231	205
%control	-	97	96	84	-	97	85	76
0-104	639	599	593	536	403	356	364	279
%control	-	94	93	84	-	88	90	69

[a]data calculated from Table 1a, pages 55-58 of registrant report.

Data on body weight gain in male and female rats shows a decrement in weight gain for male and female rats at 13 weeks in the 700 and 1500 ppm dose groups. The decrement from control rats in males is -5% and -14% for the 700 and 1500 ppm dose groups, respectively, while corresponding values in female rats are -10% and -20%. Thus, body weight gain is affected in the early phase of this study in both male and female rats, and from the above summary appears to be primarily responsible for the overall weight decrement observed in rats in the 700 and 1500 ppm dose groups.

The decrease in body weight gain for male and female rats in the 700 and 1500 ppm dose groups was evident in these dose groups throughout the duration of the study, but was most apparent in male and female rats in the 1500 ppm dose group, where the overall decrease in body weight gain compared to control was -16% and -31% for males and females, respectively. At study termination, body weight gain in the 100ppm male and female dose groups was decreased by 6% and 10%, respectively.

C. **Food Consumption and Efficiency**

Food consumption was calculated for each cage of rats on a weekly basis. Food intake per rat (g/rat/week) was calculated based on the quantity of food consumed per cage and the number of surviving rats in each cage in each week of the study. Food efficiency was calculated as the weight of food consumed per unit gain in body weight.

Group mean food consumption data are presented in **Table 4** below:

TABLE 4

Group Mean Food Consumption in Male and Female Rats Given SAN 582H in the Diet for 104 Weeks [a]

Food consumption (g/rat/week)[b]

Week of Study	Males				Females			
	0	100	700	1500	0	100	700	1500
1	235	231	226	210	180	176	175	155
13	215	218	215	203	149	156	142	144
52	216	222	213	210	155	162	153	150
78	225	250	225	242	188	186	171	183
104	226	234	233	244	214	260	229	202

[a] data from Table 2a, pages 60-63 of registrant report.

[b] group mean food consumption = total food consumed by each cage in each dose group per week / number of rats surviving in each cage.

As shown in **Table 4**, group mean food consumption in male and female rats at the 700 and 1500 ppm dose levels was decreased in comparison to control rats for weeks 1 and 13. This decrease was statistically significant based on cumulative food consumption for this time

period ($p < 0.01$, except in 700 ppm females [$p < 0.05$]; page 64 of registrant report). The early decrease in food consumption, in conjunction with the decrease in body weight gain during this period, could be the result of unpalatability of test diets at the 700 and 1500 ppm dose levels, although test article toxicity cannot be ruled out. Food consumption for the remainder of the study in male and female rats was not statistically significant from control values.

Food efficiency (total grams food consumed / total weight gain in grams) among male and female rats during the first 25 weeks of the study is shown below in the following Table (**Table 5**):

TABLE 5

Group Mean Food Efficiency in Male and Female Rats Given SAN 582H in the Diet for 104 Weeks [a]

Food efficiency (g food/g body weight gain)

Weeks	Males				Females			
of Study	0	100	700	1500	0	100	700	1500
1-5	5.5	5.5	5.6	5.9	9.2	9.0	9.8	10.7
6-10	13.0	13.8	12.8	13.9	21.3	22.8	21.7	22.0
11-15	15.6	16.9	16.6	18.6	31.6	39.3	43.4	43.3
16-20	26.7	24.4	25.6	30.7	78.3	51.4	52.8	60.5
21-25	25.5	26.5	28.2	32.0	36.7	53.8	69.7	75.1

[a]data from Table 3, page 65 of registrant report.

From the above data, it appears that food efficiency was decreased in male rats in the 1500 ppm dose group from weeks 11 through 25, while in female rats, food efficiency was decreased in the 700 and 1500 ppm dose groups from weeks 11-15, and in the 100, 700, and 1500 ppm dose groups during weeks 21-25 of the study. Overall food efficiency for weeks 1-25 of the study was decreased in 1500 ppm males vs control (13.6 vs 12.2 for weeks 1-25), and in 700 and 1500 ppm females (23.5 and 25.3 vs 21.0 overall food efficiency in 700 ppm, 1500 ppm, and 0 ppm respectively). The observation that food efficiency was affected in

male and female rats during weeks 11-25 of the study supports the conclusion of test article toxicity, as food consumption was not decreased significantly beyond week 13 of the study, and food efficiency was not significantly affected during weeks 1-10 of the study when decreases in body weight were most evident.

D. **Intake of SAN 582H**

The group mean intake of SAN 582H for male and female rats over the course of the study is summarized in the following table (**Table 6**):

TABLE 6

Group Mean Dietary Intake of SAN 582H in Male and Female Rats Over 104 Weeks[a]

Dose Group (ppm)	Nominal mg/kg/day (ppm/20)	Average Intake (weeks 1-104) (mg/kg/day) males	females
0	0	0	0
100	5.0	5.1	6.8
700	35.0	36.0	49.0
1500	75.0	80.0	109.0

[a]data taken from Table 4, pages 66-69 of registrant report.

Group mean intake of SAN 582H was between 102-106% of nominal for male rats in all dose groups over the study duration, and between 136-145% of nominal for female rats.

E. **Ophthalmoscopic Examination**

Eyes of all rats were examined prior to initiation of the study. At week 103 of the study, eyes of all surviving rats in control and 1500 ppm dose groups were examined. Examination at week 103 was extended to the 700 and 100 ppm dose groups to substantiate apparent treatment related effects observed in the 1500 ppm dose group. Ophthalmoscopic examination was performed by a qualified veterinarian using a Keeler indirect ophthalmoscope.

Three rats (1 male, 2 female) were replaced prior to dosing due to the presence of ocular lesions.

No treatment related effects on ocular status were observed at week 53 of the study in male

or female rats.

Ophthalmoscopic examination at week 103 showed an apparent treatment related exacerbation of posterior lenticular opacity in male and female rats. Four of 20 control male rats (20%) and 4 of 26 control female rats (15%) were observed with this lesion at week 103, but the incidence in males and females at 1500 ppm SAN 582H was higher (13 of 32 males, 41%; 11 of 34 females, 32%). An incidence of this magnitude has been observed previously in control rats from other studies performed by the registrant, but was considered a treatment related exacerbation of a normal age-related effect.

F. Clinical Signs and Pathology

Detailed examination of rats for any sign of ill health were recorded once a day each day for the first 5 weeks of the study. For the remainder of the study, observations were made once a week. Rats were checked on weekends for mortality.

While examining rats for clinical abnormalities, examination was also made of the appearance, location, and dimension of all palpable masses. If a mass was observed, the progression of the mass was followed by bi-monthly follow-up examination.

Blood samples were obtained from the orbital sinus of 10 male and 10 female rats from each dose group under light ether anesthesia. Samples were obtained on weeks 13, 26, 52, 78, and 104. According to the registrant (page 27 of report), blood was obtained from satellite group animals on weeks 13, 26, and 52, while blood from the main dose group on weeks 78 and 104. Where possible, the same rats were used for sampling at each time point, unless prevented by death of the animal.

Collected blood was divided into EDTA anticoagulant for hematological examination, into citrate anticoagulant for thrombotest, and into heparin anticoagulant for biochemical measurements. An Ortho ELT-1500 was utilized for hematology measurements.

a) Hematology

The following CHECKED hematological parameters were examined:

_x_ total leucocyte count*	_-_ total plasma protein*
_x_ erythrocyte count*	_x_ leukocyte differential*
_x_ hemoglobin*	_-_ mean corpuscular HGB
_x_ hematocrit*	_x_ mean corpusc. HGB conc.
_x_ platelet count	_x_ mean corpusc. volume
_x_ packed cell volume	_x_ methemoglobin
_-_ reticulocyte count	_x_ sulfa-hemoglobin

*EPA guideline requirement "-" not analyzed

Venous blood smears were prepared from all rats killed during the study, as well as from all rats killed at the interim and terminal sacrifices. Slides were fixed and stained, but examined only if considered necessary by the pathologist.

Results of hematological examination in treated male and female rats showed some statistically significant differences from controls at week 13 which included decreases in sulfa-hemoglobin in male rats at all dose levels, and a decrease in methemoglobin in male rats at the 1500 ppm dose level. Significant decreases in methemoglobin were also observed in female rats at all dose levels on week 13 of the study. While these changes were observed at week 13, subsequent hematological measurements did not reveal any relationship between dose of test article and effect on hematologic parameters, nor was there any apparent effect of time on hematology parameters as a result of test article treatment.

b) **Clinical Chemistry:**

The following CHECKED parameters were measured using a Technicon SMA 12/60 autoanalyzer and standard methodology:

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

_x_ calcium*
_x_ inorganic phosphate*
_x_ sodium*
_x_ potassium*
_x_ chloride*

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

*EPA guideline requirement "-" not examined

Note: From December of 1987, clinical chemistry measurments (except glucose) were made using a Hitachi 737 Clinical Chemistry Analyzer.

Over the course of the study, a consistent increase in gamma-glutamyl transferase which was statistically significant was observed in male rats administered 1500 ppm test article. In females, a significant increase in this enzyme was observed only at week 26.

Increased cholesterol levels were observed in females at the 1500 ppm dose group on each occasion of measurement, but this increase was significant only on week 13. No such increase was observed in male rats.

Decreased alanine and aspartate aminotransferase activities were observed in female rats in the 700 and 1500 ppm dose groups on weeks 13, 26, 52 (aspartate aminotransferase only), and 104 (alanine aminotransferase only). Male rats in these same dose groups showed a similar decrease at week 78 of the study, but at no other time point. The decrease in activities of these enzymes does not appear to be of toxicological significance, as there were no apparent dose-effect relationships seen in this decrease.

Calcium levels were significantly decreased in male rats on weeks 52 and 104 of treatment in all dose groups compared to control, but there was no apparent relationship of dose to decreases in this cation.

Other changes in electrolyte levels were noted in both male and female rats over the course of the study, some of which were significantly different from control values, but these were not considered of toxicological signficance.

c) **Urinalysis:** The following CHECKED parameters were examined:

Overnight urine samples were collected on weeks 13, 26, 52, 78, and 104 from rats which were used for collection of blood samples. The following parameters were examined:

- appearance*	x glucose*
x volume*	x pH
x specific gravity*	x bilirubin*
x protein*	x urobilinogen
x ketone*	x nitrate
x blood*	___
x sediment analysis*	___

*EPA guideline requirement "-" not examined

Results of urinalysis showed that the majority of parameters measured were not signficantly affected in test article treated rats of either sex. A small increase in urinary ketones was observed in male rats at weeks 26, 52, and 78 in the 1500 ppm dose group, but not at lower doses.

G. Macroscopic Observations

All rats were killed by carbon dioxide asphyxiation and subjected to gross necropsy. This procedure was performed at 52 weeks on all surviving rats in the satellite treatment groups, and at study termination (104 weeks) in all surviving rats in the main treatment groups.

All superficial tissues were examined visually and by palpation for evidence of tumor formation or other distortion. The external nares, buccal cavity, and tongue were then

examined, and the roof of the skull was removed to allow examination of the brain, pituitary, and cranial nerves. A ventral midline incision was then made, and skin was reflected for examination of subcutaneous tissues. During this examination, the condition of the thoracic viscera was noted, with special attention paid to the thymus, lymph nodes, and heart.

Abdominal viscera were examined before and after removal. The urinary bladder was distended with fixative, opened, and examined under low power magnification.

The stomach, cecum, and portions of the duodenum, jejunum, ileum, and colon were incised and examined. Lungs were removed and examined macroscopically. Liver was sectioned at intervals of a few millimeters for macroscopic examination, and kidneys were incised and examined.

Abnormalities in the appearance and size of the gonads, adrenals, uterus, intra-abdominal lymph nodes and accessory reproductive organs were recorded. The location, size, and multiplicity of lesions suggestive of neoplasia was recorded, as well as evidence of adhesion or invasion to adjacent structures.

Examination of rats in the satellite groups at 52 weeks for macroscopic abnormalities did not show any apparent relationship between test article administration and any macroscopic abnormalities observed in these animals.

Post mortem examination of animals in the main treatment groups revealed the following abnormalities which were considered treatment-related (**Table 7**):

TABLE 7

Macroscopic Lesions in Male and Female Rats Given Dietary SAN 582H for 104 Weeks[a]

Dose (ppm)	0		100		700		1500	
	M	F	M	F	M	F	M	F
Liver (no. examined)	50	50	50	50	50	50	50	50
-Mass/masses	1	1	0	4	0	2	4	0
-raised areas	3	5	2	2	5	5	4	2
-pale areas	6	10	5	10	14	12	17	19
-cysts	1	0	1	1	2	1	6	5
Stomach (no. examined)	50	50	50	50	50	50	50	50
-depression(s)	8	1	7	6	7	9	8	4
-thickened	3	1	2	1	2	5	2	4

TABLE 7 (cont.)

Dose (ppm)	0		100		700		1500	
	M	F	M	F	M	F	M	F
Uterus (no. examined)	-	50	-	50	-	50	-	50
-masses	-	0	-	3	-	1	-	4

[a]data taken from Table 10b, pages 96-105 of registrant report.

The number of male rats with liver masses was increased in the 1500 ppm dose group, where 4 of 50 rats were observed with masses compared to 1 of 50 in controls. Incidence of masses in the 100 and 700 ppm dose groups was similar to control. In females, liver masses found in the various treatment groups did not bear any apparent relationship to dose of test article.

Pale areas of the liver were observed to be increased in both sexes of rats at the 700 and 1500 ppm dose levels in comparison to controls. In male rats, pale areas were noted in 14 of 50 and 17 of 50 rats in the 700 and 1500 ppm dose groups, respectively, while in female rats, incidence of pale areas in these same dose groups was 12 of 50 and 19 of 50. Incidence of pale areas in control male rats was 6 of 50, and 10 of 50 in female rats.

Hepatic cysts were also an apparent result of treatment with test article. Incidence of this lesion was increased only in the 1500 ppm dose groups of males and females (6 of 50 males, 5 of 50 females) compared to controls (1 of 50 males, 0 of 50 females).

Depression and thickening of the stomach was apparently increased in female rats at all dose levels compared to control, but this lesion was apparently not felt to be related to test article treatment by the registrant.

H. Organ Weights

Organs to be weighed were obtained from all animals dying or killed during the study and dissected free of fat before weighing. The following organs from animals killed at the scheduled sacrifice were weighed: adrenals, brain, heart, kidneys, liver, spleen, testes, and ovaries, pituitary. Weights of organs from rats dying or killed during the study were recorded at the discretion of the pathologist (page 31 of registrant report). Group mean and individual organ weights were provided. Organ/body weight ratios were not provided.

Results of organ weight analysis at the interim sacrifice showed that female rats in the 700 and 1500 ppm dose groups had significantly higher liver weights in comparison to controls, when adjusted for body weight as covariate (page 41 of registrant report). Liver weight was increased to 15.4 and 15.5g in 700 and 1500 ppm females compared to 13.4g in controls ($p < 0.01$). No other significant changes in organ weight were observed in the interim sacrifice

dose groups.

Organ weight analysis at terminal sacrifice again showed a statistically significant increase in liver weight of female rats in the 1500 ppm dose group. Liver weight was increased from 17.3g in control to 19.2g in the 1500 ppm dose group ($p < 0.05$). Adrenal weight was significantly decreased in females from the 700 and 1500 ppm dose groups (81 and 83mg, respectively), but this was due to increased weight of adrenals in controls (107g). The registrant further stated (page 42) that this finding was not likely to be of toxicological significance, as there was no corrorborative histopathological evidence of abnormality.

Interestingly, pituitary weight appeared to be decreased in test article treated males and females, especially at the 700 and 1500 ppm dose levels. However, this decrease was not reported as statistically significant (pages 108-109 of registrant report).

I. Microscopic Observations

Samples of the following tissues were preserved in either 10% buffered formalin (all tissues except eyes) or Davidson's fixative (eyes). All nodules, tissue masses and macroscopically abnormal tissues were also preserved along with samples of normal tissue where appropriate.

Digestive	Respiratory	Urogenital
_x_ tongue	_x_ trachea	_x_ kidneys*
_x_ salivary glands*	_x_ lungs*	_x_ urinary bladder*
_x_ esophagus*	_x_ 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*	_x_ vagina
_x_ 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*	_x_ 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

Tissues were prepared for microscopic examination by embedding in paraffin wax, cutting thin sections (4µm), and staining with hematoxylin and eosin. Liver was cut from frozen sections at 12 µm using a cryostat and was stained for fat with Oil Red O (page 32 of report).

The tissues examined in this study fulfill the guideline requirements (83-2) for histopathological examination of tissues in a combined carcinogenicity/toxicity study (page 32 of registrant report).

Note: In addition to reading of tissue slides by the study pathologist, a routine 'peer review' was carried out by a senior pathologist at Huntingdon Research Center, and included reading and checking all individual animal reports; reading most lesions diagnosed as tumors or proliferative lesions; any unusual lesions; lesions considered contributory to the death of animals; and random spot checks of other diagnoses.

1) Neoplastic Observations

Data provided by the registrant on tumor distribution in male and female rats indicated an apparent effect of test article on the number of benign and malignant liver cell tumors in male rats, and the number of ovarian tubular adenomas in female rats. **Table 8** summarizes these data:

TABLE 8

Incidence of Neoplastic Lesions in Male and Female Rats Given Dietary SAN 582H for 104 Weeks [a]

	Males				Females			
Dose (ppm)	0	100	700	1500	0	100	700	1500
Liver								
No. of Animals Examined for Liver Tumors	50	50	50	50	50	50	50	50
Benign Liver Cell Tumor (0)	0[b] (0)[c]	0 (0)	1 (2)	3 (6)	1 (2)	1 (2)	0 (0)	0
Malignant Liver Cell Tumor	0 (0)	0 (0)	0 (0)	2 (4)	-	-	-	-
Benign+Malignant Combined	0(0)	0(0)	1(2)	4(8)	-	-	-	-
Ovaries								
Tubular Adenoma								
Animals examined	-	-	-	-	50	50	50	50
No. with Tumors	-	-	-	-	2 (4)	1(2)	2 (4)	6(12)

[a]data taken from Table12, pages 111, 119, and 120 of registrant report.

[b]number of rats with specified lesion

[c]percentage of rats with specified lesion

As shown in **Table 8**, the number of male rats with benign tumors of the liver was increased in rats treated with 700 and 1500 ppm of test article, while the number of rats with malignant tumors was increased at the 1500 ppm dose level. One-tailed statistical analysis for a positive trend against dose level showed a significant effect of increasing dose levels of test article on these lesions. Pairwise comparison of treated groups with control, however, did not reveal any significant differences. Thus, there appears to be a relationship between dose of test article and incidence of benign and malignant tumors of the liver in male rats. Although historical control data (page 44 of registrant report) show that the incidence of benign and malignant liver cell tumors in male rats covers the range of incidences from dosed male rats in this study, these data are not supportive, based upon the age of the historical control studies, and the use of a different diet in these studies (pages 43-44 of registrant report).

Thus, the increases in these types of tumors appear test article related in male rats.

In female rats receiving 1500 ppm test article for 104 weeks, the incidence of tubular adenoma of the ovaries was increased in comparison to control rats. Statistical analysis of these data revealed a similar phenomenon for this tumor type as for liver tumors in male rats (significantly positive trend with increasing dose, no significant pairwise differences). Thus, for reasons similar to those set forth for male rats, it appears that there was a relationship between increasing doses of test article and appearance of this tumor type in female rats.

2) Non-Neoplastic Observations

There were a number of apparent effects of test article treatment on non-neoplastic pathology in both male and female rats. These included (in **male** rats): increased number of altered eosinophilic hepatocytes in the liver, epithelial hyperplasia of the limiting ridge of the stomach, parathyroid hyperplasia, and (in **female** rats): bile duct hyperplasia, bile duct dilation, and tubular hyperplasia of the ovaries. A summary of these observations is included in the Table below (**Table 9**):

TABLE 9

Incidence of Non-Neoplastic Lesions in Male and Female Rats Given Dietary SAN 582H for 104 Weeks [a]

	Males				Females			
Dose (ppm)	0	100	700	1500	0	100	700	1500
No. animals examined:	50	50	50	50	-	-	-	-
Altered Eosinophilic Hepatocytes	2[b] (4)[c]	2(4)	6(12)	10(20)				
Epithelial hyperplasia (stomach)	6(12)	9(18)	8(16)	20(40)				
(No. animals examined) Parathyroid	48	45	42	44				
hyperplasia	5(10)	10(20)	13(26)	18(36)				
Bile duct hyperplasia No. animals examined:					50	50	50	50
incidence					3(6)	9(18)	11(22)	20(40)
cystically dilated					1(2)	3(6)	4(8)	7(14)

Table Table 9, cont.

Tubular hyperplasia (ovaries)				
No. animals examined:	50	50	50	50
incidence	12(24)	7(14)	14(28)	22(44)

a-data from pages 45-47 of registrant report.
b-number of rats with lesion; c-percent of rats with lesion

Note: Data on microscopic pathology for rats sacrificed at 52 weeks was provided as individual animal data in Tables 15 and 16, pages 181-201, and not in summary form as for animals in the main treatment groups. Examination of these data did not show any pertinent microscopic abnormalities related to test article treatment or dose of test article.

As shown in **Table 9** above for animals in the main treatment groups, the incidence of altered eosinophilic hepatocytes in male rats was increased from 4% in control and 100 ppm dosed rats to 12 and 20%, respectively, in 700 and 1500 ppm dosed rats. A significant (p=0.008) positive trend was noted for this effect, as was a significant (p=0.044) pairwise comparison at 1500 ppm.

Other effects observed in male rats were an increase in incidence of stomach epithelial hyperplasia, from 12% in control rats to 40% in rats at the 1500 ppm dose level (p=0.008 by pairwise comparison). A significant (p=0.007) positive trend was also found across dose levels for this alteration. Hyperplasia of the parathyroids increased from 10% in control male rats to 36% in the 1500 ppm dose group, again showing a significant positive trend across dose levels and a signficant pairwise comparison at 700 anf 1500 ppm vs control.

In female rats, bile duct hyperplasia incidence was increased in a dose-dependent manner, from 6% in controls to 40% in the 1500 ppm dose group. Significant pairwise comparisons were found at the 700 and 1500 ppm dose levels compared to control, as was a significant positive trend across doses ($p < 0.001$). A significant positive trend was found for female rats with cystically dilated bile ducts (p=0.036), but no significant pairwise comparisons were found. Ovarian tubular hyperplasia was also increased in incidence, from 24% in control rats to 28 and 44% in the 700 and 1500 ppm dose groups, respectively. A significant (p=0.003) positive trend was found across doses, as was a significant pairwise comparison at the 1500 ppm dose level compared to control (p=0.012).

III. DISCUSSION

In the present study, male and female Sprague-Dawley rats were administered SAN 582H technical in the diet for 104 weeks at levels of 0, 100, 700, and 1500 ppm in order to determine potential carcinogenicity and chronic toxicity of this compound. Rats were monitored for treatment related effects on mortality, body weight gain, food consumption, food efficiency, palpable masses, and clinical signs of toxicity. Interim sampling of blood and urine

was performed on satellite groups of treated rats to monitor toxicity during the study. At study termination, rats were killed and blood samples were again obtained for hematological analysis. Approporiate organ weights were recorded, and tissues were examined for both neoplastic and non-neoplastic changes related to treatment with test article.

Mortality in male rats was reduced between 4 and 26% at the 700 and 1500 ppm dose levels at 78 and 104 weeks of the study, while mortality in females was reduced between 4 and 10% at all dose levels at 78 weeks, and between 10 and 12% at the 700 and 1500 ppm dose levels at 104 weeks. While no explanation is readily apparent for this decrease in mortality among treated rats in the 700 and 1500 ppm dose groups, it is evident that treatment with SAN 582H did not have a negative effect on mortality on this study.

While no adverse effects were seen on mortality in this study, there were effects on body weight and body weight gain in both male and female rats. Body weight in male rats in the 700 and 1500 ppm dose groups was affected during weeks 1-10 of the study, such that body weight in these groups was decreased between 5 and 10% of control. This decrement remained in male rats until approximately 52 weeks of the study. Overall decrease in body weight gain for male rats in the 700 and 1500 ppm dose groups was 7% and 16%, respectively, for the duration of the study. A similar effect on body weight and body weight gain occurred in female rats treated with test article at the 700 and 1500 ppm dose levels. Overall decrease in body weight gain for female rats in the 700 and 1500 ppm dose groups was 10% and 30%, respectively, for the duration of the study.

The decrease in body weight gain for male and female rats at the 700 and 1500 ppm dose levels during the first 10 weeks of the study was paralleled by a decrease in food consumption in these dose groups, which suggests adverse palatability of the diet at these dose levels. However, food efficiency was not significantly affected during this time period. Efficiency of food conversion was, however, observed to decrease in male rats at the 1500 ppm dose level during weeks 11-15 of the study and until the last time point measured (25 weeks). Efficiency of food conversion was also decreased in female rats in the 700 and 1500 ppm dose groups during the same time period as male rats. Overall food efficiency was decreased in male rats at the 1500 ppm dose level, and decreased in female rats at the 700 and 1500 ppm dose levels. The observation of reduced food efficiency from week 11 to week 25 is indicative of test article toxicity, as food consumption was not decreased significantly beyond week 13 of the study, and food efficiency was not significantly affected during weeks 1-10 of the study when decreases in body weight were most evident.

Hematological effects of test article treatment were unremarkable in both male and female rats at any dose level, except on week 13, where test article treatment resulted in apparent decreases in sulfa-hemoglobin and methemoglobin in males and females. However, hematological measurements on subsequent occassions did not reveal any significant alteration in any parameter studied. Thus, SAN 582H did not appear to cause significant hematological alterations in this study.

A number of effects of test article treatment on clinical chemistry parameters were observed in both male and female rats in this study. Most notable was a significant increase in gamma-glutamyltransferase (GGT) in male rats at all times blood was sampled for analysis. This alteration was not observed in female rats, and when taken together with the finding of

altered eosinophilic hepatocytes in male rats (see below, non-neoplastic changes), is indicative of pre-neoplastic change in male rat liver. Calcium levels in male rats were also apparently altered by test article treatment. At week 13, calcium levels were significantly increased in males dosed with 1500 ppm test article, while at weeks 52 and 104, levels were decreased in the 1500 ppm dose group in relation to control values. According to the registrant (page 17 of report), there may be a relationship between decreased calcium levels observed in male rats and the increased incidence of parathyroid hyperplasia (see below) observed in male rats at the 1500 ppm dose level. Data presented in this study are not strong enough to suggest either a direct effect of test article on the parathyroid gland, or an indirect effect, possibly on parathyroid hormone. However, test article toxicity is indicated at the 1500 ppm dose level from these observations.

Clinical chemistry measurments in female rats showed a decrease in activity of both alanine and aspartate aminotransferase at the 700 and 1500 ppm dose levels on weeks 13, 26, 52, and 104 of treatment. However, these observations do not appear to be of toxicologic significance.

Analysis of urine during the study did not reveal any significant changes in any parameter measured in either male or female rats. A slight increase in urinary ketones was noted in male rats in the 1500 ppm dose group during weeks 26, 52, and 78.

Treatment-related effects on observed macroscopic lesions included an increase in liver masses in male rats at the 1500 ppm dose level, and an increase in "pale areas" in both male and female rats at the 700 and 1500 ppm dose levels (**Table 7**). An increase in hepatic cysts was also observed in female rats at the 1500 ppm dose level (**Table 7**). The increase in liver masses in male rats may bear a relationship to the increased incidence of benign liver neoplasms observed in male rats at this dose level (**Table 8**), while an increase in hepatic cysts in female rats may be related to the increased incidence of cystically dilated bile ducts observed in female rats at the 700 and 1500 ppm dose levels (**Table 9**). Epithelial hyperplasia of the stomach and increased incidence of uterine masses were also observed in female rats at the 700 and 1500 ppm dose levels.

The only significant effects of test article administration on organ weight were those on the liver. Absolute liver weights were significantly increased in female rats in the 700 and 1500 ppm dose groups sacrificed at 52 weeks, and in female rats in the 1500 ppm dose group sacrificed at study termination. However, no evidence of neoplastic or pre-neoplastic change was observed in the liver of female rats. Thus, the effect of test article on liver weight in female rats may be one of induction of microsomal protein, or other increases in protein synthesis. It is worth noting in this study that pituitary weight appeared decreased in treated male and female rats sacrificed at 104 weeks (Table 11b, page 108 of registrant report). The significance of this finding is not clear from this study. However, in light of the apparent effect of test article on parathyroid hyperplasia (see below), an effect of test article on the endocrine system cannot be completely ruled out.

The effects of test article administration on tumor formation in male and female rats was a significant finding of this study and appears related to test article administration. The incidence of benign tumors of the liver was increased in male rats over controls at the 700 and 1500 ppm dose levels, (2% and 6%, respectively, vs control incidence of 0%). Malignant tumor of the liver was also increased to 4% incidence in 1500 ppm dosed male rats vs 0% in control rats. In female rats, tubular adenomas of the ovary were present at an incidence of 12% in rats at the 1500 ppm dose level, vs 4% in controls. A statistically significant positive trend was found across doses for the incidence of these tumor types in male and female rats, supporting the conclusion of an effect of test article on tumor incidence. The registrant provided historical control data to support the conclusion that the incidence of these tumors fell within historical control range. However, two deficiencies in the historical control data weaken their support for the tumor data in this study. First, studies provided in summary form by the registrant (pages 44-45 of report) are dated from1983 to 1986, which is not representative of recent laboratory studies. Second, it is mentioned (page 43) that animals in these studies were fed a different diet than the one employed in the present study. Fullerton et al. (*Fundam. Appl. Toxicol.* **16**: 51-60, 1991) have presented evidence that diet selection in chronic carcinogenicity studies can dramatically influence tumor incidence. Thus, the historical control data cannot be considered reliable until detailed information is provided by the registrant on the composition of the two types of diets (Labsure LAD and SDS R&M No. 1) for comparison. The potential carcinogenicity of SAN 582H should be considered by the HED carcinogenicity Peer Review Committee.

Treatment of male and female rats was also apparently responsible for increases in the incidence of a number of non-neoplastic lesions. In males, an increase in altered eosinophilic hepatocytes was observed at the 700 and 1500 ppm dose levels, while epithelial hyperplasia of the stomach and parathyroid hyperplasia were observed in increased incidence at 1500 ppm test article (**Table 9**). Incidences of tubular hyperplasia of the ovaries, bile duct hyperplasia, and cystically dilated bile ducts were increased in female rats at the 700 and 1500 ppm dose levels. Significant positive trends were found for the incidences of these non-neoplastic lesions in males and females, as well as significant pairwise comparisons for all lesions except cystically dilated bile ducts in females.

The highest dose of test article examined in this study was 1500 ppm in both male and female rats. This dose caused a body weight decrement of approximately 10% during the first 13 weeks of treatment in both sexes of rats. In addition, significant histopathology of the liver and ovaries was produced in males and females respectively at the 1500 ppm dose level. Thus, this dose is considered a maximum tolerated dose (MTD) for the test article in this study.

IV. CONCLUSIONS

Technical SAN 582H was administered to male and female rats in the diet for 104 weeks at doses of 0, 100, 700, and 1500 ppm. In males, benign tumors of the liver were observed at the 700 and 1500 ppm dose levels, with an incidence of 2% and 6% in these dose groups compared to 0% in controls. In female rats, benign tubular adenomas of the ovary were observed at an incidence of 12% in the 1500 ppm dose group vs 4% in control. The

incidence of non-neoplastic alterations in the liver, parathyroid, and stomach of males and the ovary of females was also increased by treatment with test article at 700 and 1500 ppm.

Based on the effect of test article on body weight, body weight gain, and histopathology it appears that the 1500 ppm dose level was the MTD in this study.

The data in this study support the conclusion of limited evidence of carcinogenicity for technical SAN 582H, based upon the occurrence of increased incidence of benign and malignant liver tumors only in high dose male rats, and the increased incidence of tubular adenomas in female rats treated at 700 and 1500 ppm SAN 582H.

The No Observed Effect Level (NOEL) = 100 ppm

The Lowest Observed Effect Level (LEL) = 700 ppm

The Maximum Tolerated Dose (MTD) = 1500 ppm (males and females)

V. CLASSIFICATION
Core Supplementary

This study does not satisfy the guideline requirements (83-5) for a combined carcinogenicity/chronic toxicity study in rats. The following information is requested in order to upgrade this study to core minimum:

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1) The registrant is asked to provide **recent** historical control data on relevant tumor incidence from animals given the same type of diet as that used in the present study, or detailed composition of the diets used in both the historical control studies and the present study.

Statistical analysis

All statistical analyses were carried out separately for males and females.

Data relating to food and water consumption were analysed on a cage basis. For all other parameters, the analyses were carried out using the individual animal as the basic experimental unit.

Food and water consumption data were analysed using cumulative cage totals. Bodyweight data were analysed using weight gains.

The following sequence of statistical tests was used for food and water consumption, bodyweight, organ weight and clinical pathology data:

(i) If the data consisted predominantly of one particular value (relative frequency of the mode exceeded 75%), the proportion of animals with values different from the mode was analysed by appropriate methods (Fisher's and Mantel's tests (1, 2)). Otherwise:

(ii) Bartlett's test (3) was applied to test for heterogeneity of variance between treatments. Where significant (at the 1% level) heterogeneity was found, a logarithmic transformation was tried to see if a more stable variance structure could be obtained.

(iii) If no significant heterogeneity was detected (or if a satisfactory transformation was found), a one-way analysis of variance was carried out. If significant heterogeneity of variance was present, and could not be removed by a transformation, the Kruskal-Wallis analysis of ranks (4) was used.

(iv) Analyses of variance were followed by Student's 't' test and Williams' test (5) for a dose-related response, although only the one thought most appropriate for the response pattern observed was reported. The Kruskal-Wallis analyses were followed by the non-parametric equivalents of the 't' test and Williams' test (Shirley's test, (6)).

For organ weight data, analysis of covariance was used in place of analysis of variance in the above sequence. The final bodyweight was used as a covariate in an attempt to allow for differences in bodyweight which might influence the organ weights.

Prior to analysis of clinical pathology and organ weight data, the individual results were reviewed and any data exclusions were made at the discretion of the Study Director. The specific reasons were footnoted in the relevant appendices of this report.

Mortality was analysed using logrank methods (7). For selected tumours and other histopathological findings, incidence rates were analysed according to the IARC recommendations (8) and using Fisher's exact test (1). In such cases the context of observation of the tumour was determined by the pathologist. Trend tests were used, based on nominal (i.e. target) dose levels.

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Reviewed by: Alberto Protzel, Ph.D.
Review Section III, Toxicology Branch II(H7509C) Alberto Protzel 3/22/91
Secondary Review by: James N. Rowe, Ph.D.
Review Section III, Toxicology Branch II(H7509C) James N. Rowe 3/22/91

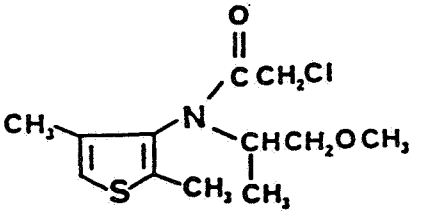
DATA EVALUATION RECORD

STUDY TYPE: Oncogenicity TOX. CHEM. NO: 195J
Species: Mouse
EPA Guideline 83-2

EPA IDENTIFICATION NO.: EPA MRID No. 416624-15 (In 8 volumes)

TEST MATERIAL: SAN 582 H

SYNONYMS/STRUCTURE: 2-chloro-N-[(1-methyl-2-methoxy)ethyl]-N-(2,4-dimethyl-thien-3-yl)acetamide



STUDY NUMBER: SDZ 346/90189

TESTING FACILITY: Huntingdon Research Centre Ltd. Huntingdon. Cambridgeshire, England.

TITLE OF REPORT: SAN 582 H. Potential tumorigenic effects in prolonged dietary administration to mice. Final Report (weeks 1 to 94).

AUTHORS: W.N. Hooks, P.R. Chambers, S.K. Majeed, W.A. Gibson, C. Gopinath, and I.S. Dawe.

REPORT ISSUED: September 13, 1990

CONCLUSIONS: SAN 582 H was administered to Crl:CD-1 (ICR) BR mice of both sexes for a period of 94 weeks in the diet at dose levels of 0, 30, 300, 1500 or 3000 ppm. SAN 582 H did not affect the distribution or rate of mortality.

Significantly decreased ($p < 0.01$) body weight gains were observed at 3000 ppm for males during the first 26 weeks of treatment, and for females during weeks 26-52 of treatment. For both sexes, the decrease in body weight gains was not statistically significant for the overall 0-94 week period.

Terminal sacrifice non-neoplastic histopathology indicated that there was a dose-related generalized hepatocyte enlargement (minimal) in treated animals of both sexes. Likewise, interim sacrifice non-neoplastic histopathology indicated an increase in centrilobular hepatocyte enlargement in high-dose animals of both sexes. In addition, interim sacrifice non-neoplastic histopathology revealed

minimal hyperkeratosis at the limiting ridge of the stomach in both sexes at 3000 ppm. This latter finding, was attributed to irritation and was not seen at terminal sacrifice.

Interim and terminal neoplastic histopathology did not reveal treatment related effects on the the incidence of tumor types or of mice with benign or malignant tumors. It is concluded that SAN 582 H is not oncogenic in Crl:CD-1 (ICR) BR mice under the conditions of this bioassay.

Based on decreased body weight gains observed in both sexes during the first year of the study and in gross and histological observations enumerated in the discussion section of this DER, it is concluded that an MTD was achieved in this study.

CLASSIFICATION: CORE MINIMUM.

A. Materials: (A photocopy of the methods is included as Appendix I).

1. Test compound: SAN 582 H. Description: brown oil. Batch No. 8605. Purity: 91.4%. Contaminants: not listed.

2. Test animals: Species: mouse. Strain: Crl:CD-1 (ICR) BR. Age: approximately 41 days (5-6 weeks) at start of dosing. Mean weight (pre-dose, -1 week): males, 24 g; females, 21 g. At the time of assignment to cages the animals were within ± 20% of the grand mean weight. Source: Charles River Ltd., Margate, Kent, England.

B. Study Design:

1. Animal assignment:

The animals were assigned randomly to the test groups shown in Table 1. A 12-day period of acclimation was allowed between allocation to groups and start of treatment.

Table 1. Dosing groups for oncogenicity study of SAN 582 H.

Group number	Dose in diet (ppm)	Main Group[1]		Satellite Group[2]	
		Males	Females	Males	Females
1 (control)	0	52	52	16	16
2	30	52	52	-	-
3	300	52	52	-	-
4	1500	52	52	-	-
5	3000	52	52	16	16

[1] Treatment group. Sacrificed after 94 weeks on treatment (Final sacrifice).
[2] Satellite group. Sacrificed after 65 weeks on treatment (Interim sacrifice).

2. Diet preparation

Diets were prepared weekly. Diets were stored within the animal room in plastic bins at an unspecified temperature, presumably room temperature. Samples of treated food were analyzed for homogeneity, concentration, and stability.

To analyze for homogeneity, duplicate random samples were obtained corresponding to the top, middle and bottom of the blended diet. As shown in Table 2, for the nominal 30 and 3000 ppm levels, blending appears to be homogeneous.

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Table 2. Analysis of blended diets for homogeneity[1].

Nominal ppm	Analyzed Concentration[2] (ppm) Top	Middle	Bottom	Mean (ppm)	Range[3] (ppm)	CV(%)
30	33.1, 31.8	31.6, 32.4	31.4, 31.6	32.0	30.6-34.0	2.02
3000	2910, 2860	2970, 2960	2920, 3010	2940	2780-3050	1.79

[1] Data obtained from Table 2, p. 1337, of the study report.
[2] Each value is the mean of duplicate analyses.
[3] Range of values for individual analyses.

To analyze for concentration, representative samples were obtained for weeks 1,13, 26, 39, 52, 65, 78, 91, and 96 of the study. As shown in Table 3, except for one value at 52 weeks, concentrations of SAN 582 H had a relative mean error in the range of -4.7% to +4.4% with respect to nominal values. At 52 weeks, analytical value for the 30 ppm nominal level had an 8% relative mean error. These values are within acceptable variability for test substance concentrations.

Table 3. Analytical concentrations of SAN 582 H during testing[1].

Week of Study	Mean analytical concentration at nominal, ppm (RME%)[2] Control	30	300	1500	3000
1	ND[3]	30.5(+1.7)	295(-1.7)	1540(+2.7)	2880(-4.0)
13	ND	30.6(+2.0)	296(-1.3)	1550(+3.3)	3000(0.0)
26	ND	30.8(+2.7)	298(-0.7)	1510(+0.7)	2930(-2.3)
39	ND	29.7(-1.0)	290(-3.3)	1500(0.0)	2880(-4.0)
52	ND	32.4(+8.0)	300(0.0)	1500(0.0)	2940(-2.0)
65	ND	30.5(+1.7)	300(0.0)	1480(-1.3)	2920(-2.7)
78	ND	30.8(+2.7)	309(+3.0)	1510(+0.7)	3040(+1.3)
91	ND	31.0(+3.3)	299(-0.3)	1470(-2.0)	2940(-2.0)
96	ND	30.6(+2.0)	299(-0.3)	1570(+4.7)	2950(-1.7)

[1] Data obtained from p. 1340 of the Study Report.
[2] RME% = Relative mean error, in percent.
[3] ND = Not detected.

The stability of SAN 582 H in formulated diets was studied using diets formulated at 30 and 3000 ppm. Formulated diets were stored under animal room conditions in polythene bags and sampled for up to 18 or 19 days. In one set of experiments the polythene bags were sealed and were placed in close proximity with each other. In another set of experiments the bags were left open and were placed at a "discrete" (unspecified) distance from each other. The results, shown in

Tables 4 (for closed bags) and 5 (for open bags), indicate that SAN 582 H is stable for at least 11 days under the conditions of the experiment. Examination of Table 4 indicates the presence of SAN 582 H in control diets after 11 days. The authors speculated that SAN 582 H appeared in the control samples as a result of translocation of the chemical from bags containing it at higher concentrations. The authors noted that in trial 1, for example, SAN 582 H appeared in the control sample and increased in the 30 ppm sample concomitant with a decrease in the concentration of SAN 582 H in the 3000 ppm bag. Likewise, in trial 2 the level of SAN 582 H in the control sample appeared to increase concomitant with a decrease in the concentration of SAN 582 H in the 3000 ppm bag. It is unclear to the reviewer, however, how the compound is translocated through the sealed polythene bags. The presence of SAN 582 H in the 0 ppm samples could reflect cross-contamination during sampling. Table 5 indicates that no such translocation has taken place.

Table 4. Stability of SAN 582 H in formulated diets. Sealed bags in close proximity. From p. 1338 of the Study Report.

Trial No.	Time stored (days)	Mean Concentration in ppm (RME %)		
		0 ppm	30 ppm	3000 ppm
1	0	ND[1]	32.0(+6.7)	2940(-2.0)
	5	ND	31.9(+6.3)	2870(-4.3)
	9	ND	33.7(+12.3)	2930(-2.3)
	18	5.68[2]	33.7(+12.3)	2830(-5.7)
2	0	ND	-[3]	3010(+0.3)
	5	ND	-	2870(-4.3)
	11	15.2	-	2870(-4.3)
	19	20.9	-	2800(-6.7)

[1] ND = Not detected.
[2] RME not given. The reported value is the average of 3.74 (analysis 1) and 7.63 (analysis 2).
[3] No data. No experiments were performed at 30 ppm.

Table 5. Stability of SAN 582 H in formulated diets. Open bags not in close proximity. From p. 1339 of the Study Report.

Trial No.	Time stored (days)	Mean Concentration in ppm (RME %)		
		0 ppm	30 ppm	3000 ppm
1	0	ND[1]	35.1(+17.0)	3010(+0.3)
	5	ND	32.7(+9.0)	2890(-3.7)
	11	ND	33.5(+11.7)	2810(-6.3)
	19	ND	30.6(+2.0)	2750(-8.3)

[1] ND = Not detected.

3. Animals were allowed free access to tap water and to SDS Rat and Mouse No. 1 (powdered) modified maintenance diet. The manufacturer was not explicitly stated.

4. Statistics - The following procedures were utilized in analyzing food consumption, body weight and organ weight data:

i) Bartlett's test to test for homogeneity of variance, at the 1% level.
ii) If no significant heterogeneity of variance was found, parametric one-way ANOVA was carried out. If significant heterogeneity was found, the Kruskal-Wallis analysis of ranks (non-parametric ANOVA) was used.
iii) Parametric ANOVA was followed by Student's 't'-test and Williams' test. The Kruskal-Wallis test was followed by the non-parametric equivalents of Student's 't'-test and Williams' test (Shirley's test).
iv) In some cases, analysis of covariance was used instead of ANOVA of organ weight data to allow for differences in body weight which might have influenced the organ weights.

Statistical analysis of the pathology findings was not done because it was not considered to be necessary by the authors.

5. Statements of data confidentiality (none claimed), adherence to GLPs and Quality Assurance inspections with signatures were included.

C. Methods and Results:

1. Observations:

Individual animals were observed at least once daily for signs of toxicity or ill health. Checks were made twice daily (morning and afternoon on weekdays, morning and mid-day on weekends and holidays) for dead and moribund animals. Mortality data are summarized in Table 6. The authors considered that SAN 582 H had not affected the distribution or rate of mortality. No statistical data were given in support of this assertion. Examination of Table 6 by the reviewer indicates

that survival in all groups was 52% or higher through week 84 of the study. In addition, survival among dosed groups appears to be no less or higher than in controls. The authors reported that there were no apparent clinical signs of a reaction to treatment during the 94-week treatment period.

Table 6. Cumulative mortality data of mice treated with SAN 582 H. Data from pp. 40 and 41 of the Study Report.

Weeks	Cumulative mortality/percent survival									
	Males (n=52/group)[1]					Females (n=52/group)				
	0	30	300	1500	3000	0	30	300	1500	3000
1-12	0/100	1/98	1/98	0/100	0/100	0/100	0/100	0/100	0/100	0/100
1-24	1/98	1/98	1/98	2/96	0/100	0/100	0/100	0/100	0/100	0/100
1-36	1/98	1/98	6/88	6/88	5/90	0/100	1/98	0/100	1/98	2/96
1-48	6/88	2/96	8/85	6/88	8/85	2/96	1/98	1/98	1/98	2/96
1-60	11/79	3/94	11/79	12/77	9/83	4/92	1/98	2/96	2/96	4/92
1-72	17/67	11/79	16/69	15/71	13/75	8/85	2/96	4/92	5/90	7/87
1-84	25/52	18/65	23/56	24/54	18/65	13/75	6/88	6/88	11/79	8/85
1-94	35/33	27/48	27/48	33/37	28/46	19/63	11/79	11/79	18/65	14/73

[1] Initial number.

2. Body weight:

The animals were weighed at the time of assignment of the animals to groups, seven days before the start of treatment, on the first day of treatment, and weekly thereafter. Table 7 shows the group mean body weights and Table 8 shows mean body weight gains during treatment. Significantly decreased ($p < 0.01$) body weight gains were observed during the first 26 weeks of treatment for males at 3000 ppm. During weeks 0-26, mean male body weight gains at 3000 ppm were decreased by 28% relative to controls (Table 8). The decrease in body weight gain appeared to be generally dose dependent. The effect was also transient because it was not observed for the 26-52 or the 0-94 week periods. Significantly decreased ($p<0.01$) mean female body weight gains were observed during weeks 26-52 in females at 3000 ppm. Over the period of weeks 0-52, mean female body weight gains at 3000 ppm were decreased by 28.9% relative to controls (Table 8). The decrease in female body weight gains appeared to be generally dose-dependant over the 0-52 week period (i.e. 12.3% at 30 ppm, 6.1% at 300 ppm, 15.8% at 1500 ppm and 28.9% at 3000 ppm).

Table 7. Group mean body weights of mice treated with SAN 582 H. Data abstracted from pp. 42-45 of Study Report.

Week	Group mean body weights (g)									
	Males (n=52/group)					Females (n=52/group)				
	0	30	300	1500	3000	0	30	300	1500	3000
0	29	28	28	28	29	23	23	22	22	23
13	39	39	39	38	38	28	28	28	28	28
26	42	43	40	41	38	31	30	31	31	30
39	44	45	44	42	42	33	32	33	32	32
52	44	46	44	42	42	34	33	33	32	31
65	46	47	45	44	44	36	35	35	35	34
78	47	46	45	44	42	37	36	35	35	34
94	43	46	43	43	41	35	35	35	33	33

Table 8. Group mean body weight gains of mice treated with SAN 582 H. Data from p. 46 of Study Report.

Week	Group mean body weight gains(g)									
	Males (n=52/group)					Females (n=52/group)				
	0	30	300	1500	3000	0	30	300	1500	3000
0 -13	10.3	11.4	11.5	10.0	9.1*	5.5	5.4	5.7	5.6	5.0
SD	3.63	3.44	2.49	2.90	2.79	2.28	2.60	2.18	2.39	2.10
13-26	2.9	4.0	0.6**	2.1**	0.5**	2.3	2.5	3.2	2.8	2.4
SD	2.19	3.35	2.76	2.04	2.84	2.43	2.80	2.91	2.31	1.96
0-26	13.3	15.4	12.1	12.4	9.6**	7.8	7.9	8.9	8.4	7.4
SD	4.63	4.80	3.90	2.73	3.83	3.35	3.96	3.72	3.39	2.81
26-52	2.4	2.0	3.6	1.4	3.4	3.5	2.1*	1.7*	1.3**	0.7**
SD	3.37	2.64	3.13	3.48	2.80	3.82	3.02	2.03	2.55	2.26
0-52	16.0	17.6	16.3	13.9*	13.6**	11.4	10.0	10.7	9.6*	8.1**
SD	4.86	5.18	3.94	4.84	2.64	4.87	4.83	4.41	5.07	3.53
0-94	15.1	17.9	15.6	15.5	12.4	12.4	12.5	12.2	10.6	10.2
SD	7.22	6.22	5.60	3.72	3.13	5.80	5.35	5.79	6.28	4.27

* P<0.05, with respect to controls, Williams' test.
** P<0.01, with respect to controls, Williams' test.

3. Food consumption and compound intake:

The quantity of food consumed was determined weekly. Compound intake (mg/kg/day) was calculated from the group mean body weights, the food consumption data, and the nominal dietary inclusion levels of the test compound. As shown in Table 9, although food consumption in 3000 ppm males was somewhat decreased with respect to controls at 14-26 weeks (93% of controls), there were no statistically significant differences in food consumption among males. Among females at 3000 ppm, there was a statistically significant decrease in food consumtion (93% of controls) during weeks 27-52. Mean compound intake over the course of the study (mg/kg b. wt./day) was proportionally increased in both sexes as follows:

- Males: 3.8, 40.8, 205, 431 for 30, 300, 1500, and 3000 ppm, respectively. (From p. 56 of the Study Report).
- Females: 4.1, 40.1, 200, 411 for 30, 300, 1500, and 3000 ppm, respectively. (From p. 56 of the Study Report).

Table 9. Food consumption (g/mouse/period) of mice treated with SAN 582 H. Data copied from p. 51 of the Study Report.

Week range	Group and dosage (ppm)									
	1♂ Control	2♂ 30	3♂ 300	4♂ 1500	5♂ 3000	1♀ Control	2♀ 30	3♀ 300	4♀ 1500	5♀ 3000
1-13	478	465	480	469	479	402	400	393	392	403
SD	55.5	29.7	42.9	27.7	57.7	28.2	28.4	25.6	32.0	38.0
% of Control	-	97	100	98	100	-	100	98	98	100
14-26	524	514	510	500	488	416	402	407	399	393
SD	91.6	87.1	63.5	58.5	65.9	33.5	36.5	33.8	36.4	34.7
% of Control	-	98	97	95	93	-	97	98	96	94
1-26	1002	979	990	969	968	818	802	800	791	796
SD	143.5	113.8	104.9	75.1	118.3	58.0	61.4	56.3	65.8	67.9
% of Control	-	98	99	97	97	-	98	98	97	97
27-52	1078	1007	1066	1075	1074	804	785	779	767	748 *
SD	175.8	165.1	125.6	183.6	209.9	77.1	80.3	78.9	48.6	57.2
% of Control	-	93	99	100	100	-	98	97	95	93
1-52	2080	1986	2056	2045	2041	1622	1587	1579	1558	1545
SD	310.8	275.4	220.0	233.6	317.7	131.4	135.0	126.8	104.5	117.4
% of Control	-	95	99	98	98	-	98	97	96	95
1-94	3544	3693	3793	3722	3912	2896	2860	2840	2784	2864
SD	432.9	515.1	411.6	370.6	708.9	260.9	270.2	251.2	186.0	343.1
% of Control	-	104	107	105	110	-	99	98	96	99

SD Standard deviation
Level of significance in comparison to control (Williams' test): * P<0.05

4. Opthalmological examinations:

No eye examinations were performed (not required).

5. a. Hematology:

Venous blood smears were prepared, if possible, from all mice killed during the study, and from all survivors from each group in weeks 52, 78, and immediately before termination (Week 66, interim sacrifice and week 95, terminal sacrifice). Differential white blood cell (WBC) counts performed on all mice in the control and 3000 ppm groups in weeks 52, 65 (interim sacrifice), 78/79, and 95 (final sacrifice) revealed no treatment-related effects. Differential WBC counts for the interim and final sacrifice periods are shown in Table 10.

Table 10. Differential white blood cell counts[1] of control and 3000 ppm mice at 65 and 95 weeks. Data copied from pages 58 and 60 of the study report.

Week 65 (26 January 1989)

Group/ dosage ppm	WBC %				
	N	L	E	B	M
1♂ Control	50	45	5	0	0
5♂ 3000	51	45	4	0	0
1♀ Control	33	63	4	0	0
5♀ 3000	39	57	4	0	0

Week 95 (24 August 1989)

Group/ dosage ppm	WBC %				
	N	L	E	B	M
1♂ Control	49	44	7	0	0
5♂ 3000	46	46	8	0	0
1♀ Control	38	58	4	0	0
5♀ 3000	33	61	5	0	0

[1] N = neutrophiles; L = lymphocytes; E = eosinophiles; B = basophiles; M = Monocytes.

5b. Clinical Chemistry.

No clinical chemistry parameters were reported (none are required by EPA Guideline 83-2).

6. Urinalysis.

No urinalysis data were reported (none are required by EPA Guideline 83-2).

7. Sacrifice and Pathology:

All animals chat died and that were sacrificed on schedule were subject to gross pathological examination and the CHECKED (X) tissues listed below were collected for histological examination. The DOUBLE-CHECKED (XX) organs, in addition, were weighed.

Digestive System		**Cardiovasc./Hemato.**		**Neurologic**	
X	Tongue	X	Aorta	XX	Brain*+
X	Salivary glands*	XX	Heart*+	X	Periph. nerve (sciatic)*
X	Esophagus*	X	Bone marrow[1]	X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	X	Eyes
X	Duodenum*	XX	Spleen*+		Eyes (optic n.)
X	Jejunum*	X	Thymus*	**Glandular**	
X	Ileum*	**Urogenital**		XX	Adrenal gland*+
X	Cecum*	XX	Kidneys*+	X	Lacrimal gland
X	Colon*	X	Urinary bladder*	X	Mammary gland*
X	Rectum*	XX	Testes*+	X	Parathyroid*
		X	Seminal vesicles	X	Pituitary*
XX	Liver*+	X	Epididymides[2]	X	Thyroid*
X	Gall bladder*	X	Prostate	**Other**	
X	Pancreas*	X	Uterus*	X	Bone (with b. marrow)*
Respiratory		X	Ovaries*	X	Skeletal muscle*
X	Trachea*		Oviduct	X	Skin*
X	Lungs*+	X	Vagina*	X	All gross lesions and masses*
X	Nose			X	Harderian gland
X	Pharynx			X	Head (to preserve nasal cavity, paranasal sinuses, oral cavity lacrymal and Zymbal's gland).
X	Larynx				
X	Nasal turbinates				

* Required for oncogenicity studies (EPA Guideline 83-2).
\+ Organ weights required in oncogenicity studies (EPA Guideline 83-2).
[1] Sternum was removed for both bone and marrow.
[2] Removed with testes.

a. Organ weights

A summary of mean male/female organ weights (g) is presented below in Table 11 for the interim and final sacrifice periods. For the interim sacrifice, a significant elevation of liver weights in both sexes was observed. For the terminal sacrifice (week 95), significantly elevated ($p<0.01$) liver and kidney weights were observed in females at 1500 and 3000 ppm.

Table 11. Mean organ weights at interim and final sacrifice. (Data from Table 7, pp. 61-64, of the Study Report.

Organ	Mean male/female organ weights (g)				
	Control	30 ppm	300 ppm	1500 ppm	3000 ppm
Interim sacrifice (65 weeks of dosing):					
Brain	0.502/0.481	-[1]	-	-	0.472*[2] /0.458
Heart	0.270/0.152	-	-	-	0.260/0.154
	(0.274/0.150)[3]	-	-	-	(0.257/0.156)
Liver	2.52/1.66	-	-	-	3.07/2.02
	(2.61)/[1.62]	-	-	-	(3.00*)/[2.04***]
Kidneys	0.896/0.437	-	-	-	0.980/0.486*
Adrenal	7.9/8.8	-	-	-	7.7/8.1
	(--[4]/8.4)	-	-	-	(--/7.8)
Testes	3.61/N.A.[5]	-	-	-	(0.337/N.A.)
Terminal sacrifice (94 weeks of dosing):					
Brain	0.495/ 0.500	0.489/0.503	0.495/0.497	0.483/0.490	0.480/0.486
Heart	0.287/0.181	0.277/0.170	0.301/0.178	0.295/0.175	0.292/0.174
	(0.285/0.179)	(0.271/0.169)	(0.304/0.177)	(0.297/0.178)	(0.296/0.176)
Liver	2.75/1.77	2.57/1.80	2.92/1.80	3.09/2.14**	3.08/2.08**
	[--/1.71]	[--/1.73]	[--/1.76]	[--/2.14**]	[--/2.09**]
Kidneys	0.882/0.483	0.850/0.471	0.891/0.488	0.901/0.545**	0.932/0.550**
	[--/0.471]	[--/0.458]	[--/0.482]	[--/0.546**]	[--/0.550**]
Adrenal	6.5/11.0	7.9/12.0	7.9/11.3	10.5***/10.2	8.0/11.6
Testes	0.360/N.A.	0.345/N.A.	0.337/N.A.	0.354/N.A.	0.352/N.A.
	(0.359/N.A.)	(0.34/N.A.)	(0.339/N.A.)	(0.355/N.A.)	(0.355/N.A.)

[1] "-" = No data. Only controls and 3000 pmm mice were interim-sacrificed.
[2] * = $p<0.05$; ** = $p<0.01$; *** = $p<0.001$.
[3] Numbers in parenthesis, (), are bodyweight-adjusted means. Numbers in brackets, [], are back-transformed means after a log transformation for analysis of the data.
[4] -- = No data.
[5] "N.A." = Not applicable.

b. Gross pathology

Gross pathology examination of animals sacrificed in extremis during the dosing phase and in the Interim (After 66 weeks of dosing) and Terminal (After 94 weeks of dosing) sacrifices revealed no significant differences with respect to controls.

c. Microscopic pathology

Selected microscopic pathology findings for the interim sacrifice (65 weeks of dosing) are shown below in Table 12. Microscopic pathology examination revealed centrilobular hepatocyte enlargement and minimal hyperkeratosis at the limiting ridge of the stomach in both sexes at 3000 ppm. This latter finding, was attributed to irritation and was not seen at terminal sacrifice. No significant treatment-related neoplastic changes were observed.

Table 12. Selected microscopic pathology findings for the interim sacrifice (65 weeks of dosing). Data from pp. 79-96 of the Study Report.

Finding	Incidence			
	Males		Females	
	Control	3000 ppm	Control	3000 ppm
LIVER				
No. Examined	12	13	16	15
Benign liver cell tumor	3	2	-[1]	-
Malignant liver cell tumor	1	0	-	-
Centrilobular hepatocyte enlargement (Total; minimal)	0	3	0	8
Enlarged hepatocytes	0	1	-	-
Vacuolated hepatocytes (Total; min.)	0	2	1	0
Centrilobular hepatocyte vacuolation (Total; minimal)	5	4	3	8
STOMACH				
No. Examined	12	13	16	15
Hyperkeratosis at the limiting ridge (Total; minimal)	0	6	4	9
Hyperplastic gastritis - glandular region (Total)	2	0	0	1
Gastric hyperplasia (Total)	1	2	2	0
Amyloid - glandular region	0	1	0	1
LUNG				
No. Examined	12	13	16	15
Adenoma	3	3	0	2
Adenocarcinoma	-	-	1	0

[1] No data.

Selected microscopic pathology findings for the terminal sacrifice (upon completion of the 94-week treatment period) are shown in Tables 13 to 16.

Terminal microscopic pathology examination of non-neoplastic lesions revealed dose-dependent minimal hepatocyte enlargement in males (Table 13; 3/52 in control vs 1/52 at 30 ppm, 7/52 at 300 ppm, 8/51 at 1500 ppm, and 27/51 at 3000 ppm) and in females (Table 14; 0/52 in controls vs 2/52 at 30 ppm, 6/52 at 300 ppm, 15/52 at 1500 ppm, and 31/52 at 3000 ppm). In addition, in males, there were apparent elevations (Table 13) in myocardial scarring (2/52 in controls vs 8/52 at 30 ppm, 6/52 at 300 ppm, 8/51 at 1500 ppm, and 9/51 at 3000 ppm), in kidney cortical mineralization (1/51 in control vs 8/51 at 3000 ppm), and in kidney cortical tubular basophilia and tubular loss (0/52 in controls, 4/52 at 30 ppm, 9/52 at 300 ppm, 5/51 at 1500 ppm and 4/51 at 3000 ppm). In females, there were apparent elevations in cortical tubular basophilia and tubular loss (Table 14; 0/52 in controls, 4/52 at 30 ppm, 5/52 at 300 ppm, 2/52 at 1500 ppm, and 4/52 at 3000 ppm).

Selected findings for terminal microscopic pathology examination of neoplastic lesions are presented in Tables 15 and 16. Historical control data were not submitted.

The incidence of benign liver tumors in males (1/animal) did not appear to be dose-related (Table 15; 5/52 in controls, 8/52 at 30 ppm, 7/52 at 300 ppm, 5/51 at 1500 ppm, and 5/51 at 3000 ppm). Two benign liver tumors/ animal were observed with an incidence of 0/52 in controls vs 2/52 at both 30 and 300 ppm, 1/52 at 1500 ppm and 2/52 at 3000 ppm. Likewise, the incidence of malignant liver cell tumors (1/animal) did not appear to be dose-related (Table 15; 3/52 in controls, 4/52 at 300 ppm, 4/51 at 1500 ppm, and 0/51 at 3000 ppm). No instances of 2 malignant ~~liver tumors/animal were found~~ at the 1500 or 3000 ppm doses. In females (Table 16), the incidence of benign liver cell tumors (1/animal) amounted to 1/52 in controls and in 30 and 1500 ppm animals; and to 0/52 at 300 and 3000 ppm.

Pulmonary adenomas were present both in controls and treated animals but there was no evidence of a compound- or dose-related effect.

Pheochromocytoma, thyroid follicular adenoma, histiocytic sarcoma and other neoplastic findings were observed in treated animals but were not dose related (Tables 15-16). These neoplastic findings were said to show no significant deviation from th e expected tumor profile mice of the strain used in the study. No historical tumor data were submitted to allow reviewer's verification of this assertion by the authors.

Table 13. Selected microscopic non-neoplastic findings in males at terminal sacrifice. Data from pp. 126-152 of the Study Report.

	Incidence of non-neoplastic findings at terminal sacrifice									
	Control		30 ppm		300 ppm		1500 ppm		3000pp	
Finding	D	T	D	T	D	T	D	T	D	T
MALES COMPLETED	37	15	28	24	27	25	33	19	30	22
HEART										
Examined	37	15	28	24	27	25	32	19	29	22
Atrial thrombus	2	0	2	0	3	0	4	1	3	2
Myocardial scarring	2	0	8	0	4	2	5	3	4	5
LIVER										
Examined	37	15	28	24	27	25	32	19	29	22
Enlarged hepatoc. (Min.)	0	3	0	1	0	7	2	6	8	19
Enlarged hepatoc. (Mod.)	0	0	0	0	0	1	1	0	0	0
Centrilobular hepatoc. enlargment (Minimal)	1	0	2	1	0	1	3	2	3	0
Centrilobular enlarg. and vacuolation:										
Minimal:	0	0	0	1	1	6	1	4	0	0
Moderate:	0	0	0	0	0	1	0	0	0	0
Centrilobular hepatoc. vacuolation:										
Minimal:	2	5	2	10	0	9	1	6	0	3
Moderate:	0	0	0	1	0	0	0	0	0	0
KIDNEY										
Examined	37	15	28	24	27	25	32	19	29	22
Cortical mineralization	1	0	0	3	0	2	1	1	2	6
Cortic. tubular basophilia and tubular loss	0	0	1	3	2	7	0	5	0	4

Table 14. Selected microscopic non-neoplastic findings in females at terminal sacrifice. Data from pp. 153-174 of the Study Report.

	Incidence of non-neoplastic findings at terminal sacrifice									
	Control		30 ppm		300 ppm		1500 ppm		3000pp	
Finding	D	T	D	T	D	T	D	T	D	T
FEMALES COMPLETED	19	33	11	41	11	41	18	34	15	37
HEART										
Examined	19	33	11	41	11	41	18	34	15	37
Atrial thrombus	1	0	0	0	0	0	2	1	2	0
Myocardial scarring	0	0	0	0	0	0	1	0	0	1
LIVER										
Examined	19	33	11	41	11	41	18	34	15	37
Enlarged hepatocytes (generalized) minimal	0	0	0	2	1	5	1	14	2	29
Centrilobular hepatocyte enlargement (Tot.) min.	0	0	0	0	0	0	3	1	1	1
KIDNEYS										
Examined	19	33	11	41	11	41	18	34	15	37
Cortical mineralization	1	0	0	1	0	0	0	0	0	0
Cortical tubular basophilia and tub. loss	0	0	0	4	0	5	0	2	1	3
STOMACH										
Examined	19	33	11	41	11	41	18	34	15	37
Hyperkeratosis of the limiting ridge:										
Minimal:	1	0	0	4	0	1	0	0	0	5
Moderate	0	0	1	1	0	0	0	0	0	1

Table 15. Selected microscopic neoplastic findings in males at terminal sacrifice. Data from pp. 104-113 of the Study Report.

Finding	Incidence of neoplastic findings at terminal sacrifice									
	Control		30 ppm		300 ppm		1500 ppm		3000pp	
	D	T	D	T	D	T	D	T	D	T
MALES COMPLETED:	37	15	28	24	27	25	33	19	30	22
MULTICENTRIC TUMORS										
Examined	4	1	3	0	0	0	2	0	3	1
Malignant lymphoma	3	1	0	0	0	0	2	0	2	0
Pleomorphic lymphoma	0	0	2	0	0	0	0	0	0	1
Myeloid leukemia	0	0	0	0	0	0	0	0	1	0
Histiocytic sarcoma	0	0	1	0	0	0	0	0	0	0
LIVER										
Examined	37	15	28	24	27	25	32	19	29	22
Benign liver cell tumor	2	3	4	4	2	5	0	5	0	5
Two benign l.c.[1] tumors	0	0	1	1	1	1	1	0	2	0
Three benign l.c. tumors	0	0	0	0	0	0	1	0	0	0
Malignant l.c. tumor	1	2	1	0	1	3	2	2	0	0
Two malignant l.c. tumors	0	0	1	0	0	1	0	0	0	0
Hemangioma	0	0	0	0	0	0	1	0	0	0
Hemangiosarcoma	0	0	0	0	0	0	1	0	0	0
LUNGS										
Examined	37	15	28	34	27	25	32	19	29	22
Pulmonary adenoma	4	3	4	5	0	6	4	6	0	7
Two pulmonary adenomata	4	0	0	0	1	2	1	1	0	1
Pulmonary adenocarcinoma	0	1	1	6	2	4	0	0	1	2
Two pulmon. adenocarc.	1	0	0	1	0	0	0	0	0	0
ADRENALS										
Examined	37	14	28	24	27	25	32	19	29	22
Phaeochromocytoma	0	0	0	0	0	0	0	1	0	0
THYROID										
Examined	37	15	28	24	27	25	32	19	29	22
Follicular adenoma	0	0	0	1	1	0	0	0	0	0

[1] l.c.= liver cell.

Table 16. Selected microscopic neoplastic findings in females at terminal sacrifice. Data from pp. 114-125 of the Study Report.

	Incidence of neoplastic findings at terminal sacrifice									
	Control		30 ppm		300 ppm		1500 ppm		3000pp	
Finding	D	T	D	T	D	T	D	T	D	T
FEMALES COMPLETED	19	33	11	41	11	41	18	34	15	37
MULTICENTRIC TUMORS										
Examined	9	6	3	11	7	11	7	10	5	7
Malignant lymphoma	5	6	2	9	2	8	5	8	2	4
Pleomorphic lymphoma	3	0	0	2	2	3	0	2	1	1
Lymphoid leukemia	0	0	0	0	0	0	1	0	0	0
Histiocytic sarcoma	1	0	1	0	2	0	1	0	2	2
LIVER										
Examined	19	33	11	41	11	41	18	34	15	37
Benign liver cell tumor	0	1	0	1	0	0	0	1	0	0
Hemangioma	0	0	0	0	0	0	0	0	1	0
LUNGS										
Examined	19	33	11	41	11	41	18	34	15	37
Pulmonary adenoma	2	1	1	5	0	7	0	3	0	4
Pulmonary adenocarcinoma	1	2	0	2	0	3	2	1	2	2
Two Pulmon. adenocarcin.	0	0	0	0	0	1	0	0	0	1
ADRENALS										
Examined	19	33	11	41	11	41	18	34	15	37
Pheochromocytoma	0	0	0	0	0	0	0	0	0	1
THYROID										
Examined	19	33	11	41	10	41	18	34	15	37
Follicular adenoma	0	0	0	0	0	0	0	0	0	1

D. Discussion:

SAN 582 H was administered to Crl:CD-1 (ICR) BR mice of both sexes for a period of up to 95 weeks in the diet at dose levels of 0, 30, 300, 1500 or 3000 ppm.

Significantly decreased ($p < 0.01$) body weight gains were observed during the first 26 weeks of treatment for males at 3000 ppm. During weeks 0-26, mean male body weight gains at 3000 ppm were decreased by 27.8% relative to controls (Table 7). The decrease in body weight gain, which appeared to be generally dose dependent, was not observed for the 26-52 or the overall 0-94 week periods. Significantly decreased ($p<0.01$) mean female body weight gains were observed during weeks 26-52 in females at 3000 ppm. Over the period of weeks 0-52, mean female body weight gains at 3000 ppm were decreased by 28.9% relative to controls (Table 8). The decrease in female body weight gains appeared to be generally dose-dependant over

the 0-52 week period (i.e. 12.3% at 30 ppm, 6.1% at 300 ppm, 15.8% at 1500 ppm and 28.9% at 3000 ppm). The decrease in female body weight gains was not statistically significant for the overall 0-94 week period. There were no significant differences in food consumption compared to controls.

Terminal sacrifice non-neoplastic histopathology indicated that there was a dose-related generalized hepatocyte enlargement (minimal) in treated animals of both sexes. Likewise, interim sacrifice non-neoplastic histopathology indicated an increase in centrilobular hepatocyte enlargement in high-dose animals of both sexes. In addition, interim sacrifice non-neoplastic histopathology revealed minimal hyperkeratosis at the limiting ridge of the stomach in both sexes at 3000 ppm. This latter finding, was attributed to irritation and was not seen at terminal sacrifice.

Interim and terminal neoplastic histopathology did not reveal treatment related effects on the the incidence of tumor types or of mice with benign or malignant tumors.

Based on:

1. Decreased body weight gains in both sexes during the first year of treatment.
2. Dose related hepatocyte enlargement in both sexes.
3. Elevation in liver weights (both sexes) at the interim sacrifice and elevation in liver and kidney weights in females at terminal sacrifice.
4. Minimal hyperkeratosis of the limiting ridge of the stomach (both sexes) at the highest dose (3000 ppm) at the interim sacrifice.

It is concluded that an MTD was achieved in this study.

8315

Appendixes

Appendix 1. Experimental Procedure.

DIMETHENAMID RIN 2014-93

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