(23) Attachment B

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Data Evaluation Report

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

EPA ID Numbers: MRID number: 415920-04
Caswell No: 003B-ICI
HED Project Nos: 0-1999

Test material: SC-5676

Synonyms: 2-chloro-N-(ethoxymethyl)-N-(2-ethyl-6-methylphenyl)acetamide;
Acetochlor

Study number(s): 88/SUC017/0348

Sponsor: ICI Central Toxicology Laboratory
Macclesfield
Cheshire, UK

Testing Facility: Life Science Research, Ltd.
Suffolk, England

Title of report: SC-5676: Combined Oncogenicity and Toxicity Study in Dietary Administration to CD Rats for 104 Weeks

Author(s): D.M. Virgo (senior author); Alan Broadmeadow (study director)

Study Completed: March 18, 1988

Conclusions:

Technical SC-5676 was administered to male and female rats in the diet for 104 weeks at doses of 0, 18, 175, and 1750 ppm (0, 0.8, 7.9, and 79.6 mg/kg/day active ingredient). In males and females,systemic toxicity in the form of reduced body weight gain, decreased food efficiency, opthalmologic abnormalities, elevated GGT and cholesterol, and increased organ:body weight ratios were evident at the 1750ppm dose level, establishing this as a maximum tolerated dose for the study. Tumorigenic responses were observed in both sexes from administration of

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1750ppm SC-5676. These included a significant increase in the incidence of nasal epithelial adenomas and thyroid follicular cell adenomas. Nasal carcinomas were observed in a total of 3 rats (2 males and 1 female). Rare tumors in the form of chondroma of the femur and basal cell tumors of the stomach were also observed. Non-neoplastic histopathology in the kidney, retina, pancreas, and nasal epithelium was also increased at the 1750ppm dose level.

The data in this study support the conclusion of limited evidence of carcinogenicity for technical SC-5676, based upon the occurrence of increased incidence of benign thyroid follicular cell tumors and benign and malignant nasal tumors only in high dose male and female rats, and the occurrence of benign chondroma and basal cell tumors in male and female rats.

The No Observed Effect Level (NOEL) = 175 ppm

The Lowest Observed Effect Level (LEL) = 1750 ppm (males and females; decreased body weight gain, decreased food efficiency, increased organ:body weight ratios, increased plasma GGT and cholesterol).

The Maximum Tolerated Dose (MTD) = 1750 ppm (males and females; decreased body weight gain).

Classification: Core Minimum

This study satisfies the guideline requirements (83-5) for a combined carcinogenicity/ chronic toxicity study in rats.

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I. MATERIALS AND METHODS

A. Test Material

SC-5676; description:dark brown viscous liquid oil (batch #s 1 and 3); Purity (by pre-study analysis provided by sponsor: 91.0% [page 285 of report]).

Test article was stated as stable under the storage conditions employed. This was verified from analysis of samples of test material obtained prior to and following the study by ICI Western Research Laboratories, Richmond, California. Results of this analysis (pages 285-286) demonstrated the stability of test material under the storage conditions employed by the performing laboratory.Test material was found to be stable in rodent diet when kept at -20 °C, but was shown to have limited shelf life (between 8-11 days; page 292 of report). Thus, test diets were prepared weekly.

B. Test Animals

Two hundred ninety four male and 295 female CD rats (remote Sprague-Dawley origin) Source: Charles River U.K. Limited, Kent, England. Age: approximately 4-5 weeks old upon receipt. Weight range (at time of dosing): males, 108-170g; females, 98-153g.

C. Animal Husbandry

A total of 589 rats (294 males and 295 females) were employed in this study. On arrival, rats were assigned to treatment groups at random and individually identified. Health status of the rats was assessed daily during the 9 day acclimation period prior to commencement of dosing. During the first 54 weeks of treatment, rats were housed in polypropylene cages measuring 38 x 25 x 18cm. From week 55 onward, rats were housed in similar cages with dimensions of 45 x 28 x 20cm. into suspended cages with wire mesh floors so that each cage contained 5 rats of the same sex.

All rats had free access to food (Labsure Laboratory Animal Diet No. 2, Cambridgeshire) which was ground by the manufacturer. Water in polyethylene bottles was also supplied *ad libitum*. Food and water were withheld only overnight preceeding blood or urine collection. Animals were housed in temperature (18 - 25 °C) and humidity (40 - 70%) controlled rooms, and permanent daily recordings were made of these parameters. A 12 hour light/dark cycle was employed. No significant deviations in these parameters was observed during the study.

Cages were dispersed so that possible environmental influences arising from their distribution were equilibrated.

D. Dietary Mixtures

SC-5676 was administered by admixture with the diet in powdered form. Dietary pre-mixes were prepared weekly by incorporation of a weighed quantity of SC-5676 into untreated test diet. This premix was stirred for

20 minutes in a Hobart A200 mixer, and was then further diluted with test diet to give a final concentration of technical material of 1750ppm. Mixing at this stage was continued for 15 minutes in a Gardner 50L mixer. This diet was used for the high dose group, while serial dilution of this prepared diet was performed to attain the dosing concentrations of test article for other treatment groups.

D. Stability and Homogeneity

Stability of dietary test mixtures was performed on trial diets prior to study initiation. A trial dietary mixture of 18ppm was prepared and sampled for analysis prior to the study. Stability was checked after storing the diet at room temperature for 7, 10, and 14 days, as well as after storage for four days at -20 °C followed by 3 and 11 days storage at room temperature. Results of this analysis (page292 of report) showed a usable shelf life of between 10-11 days when stored at room temperature (i.e. found concentration within 10% of nominal). No alteration in test diet concentration resulted from storage at -20 °C. Therefore, diets were prepared weekly, and each prepared batch was divided into two batches, of which the first was used for days 1-4 of the week, and the second batch stored at -20 °C until used on the last 3 treatment days of the week.

Representative samples (100g) of test diets were taken at weeks 1, 2, 3, and 4, and at four week intervals thereafter to assess achieved concentration of test diet over the course of the study. Results of analysis for achieved concentration of test article (page 301 of report) showed the following results:

	Range (% nominal)	Mean (% nominal)
Group 2 (low dose):	92-114	101± 5.7
Group 3 (mid dose):	87-109	97 ± 5.3
Group 4 (high dose):	84-107	98 ± 5.4

Homogeneity of dietary test mixtures at the low and high dose level was conducted in representative samples taken from six positions in the mixer. Results of this analysis (page 291 of report) showed that the concentration of test material at the six positions sampled for each dose level was within 10% of the nominal concentration for each dose level.

E. Experimental Design and Dosing

Rats were assigned to one of eight dose groups. Tumorigenic potential of SC-5676 was assessed in groups of fifty males and 50 females who received test chemical for 104 weeks in the diet at the following four dose levels:

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Group #	Dose Level (ppm)	No. of Rats male	female
1	0	50	50
2	18	50	50
3	175	50	50
4	1750	50	50

In addition to the above, a further ten males and females were treated at the 18 and 175ppm dose levels for 52 weeks, as were a group of 20 males and females at the 0 and 1750ppm dose levels.

Dose levels for this study were selected based upon results obtained from a subchronic oral toxicity study in rats (MRID# 415920-04) in which dietary levels of 0, 20, 200, and 2000ppm test article were used.

It was not stated whether rats were housed within the same animal room for the entire course of the study. SC-5676 was administered continuously in the diet to treatment groups. Control rats received untreated diet of the same batch and at the same frequency as test article treated rats.

An additional 10 male and female rats were selected from the total rats ordered and used as veterinary controls to monitor the potential outbreak of disease during the study. According to the registrant (page 18), no outbreak of disease occurred during the study.

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. **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 SC-5676 in the Diet for 104 Weeks[a]

Week of Study	Males				Females			
	0	18	175	1750	0	18	175	1750
1	0(0)[b]	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
13	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	1(2)
26	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	3(6)
52	1(2)	0(0)	1(2)	0(0)	0(0)	2(4)	1(0)	5(10)
78	13(26)	10(20)	10(20)	8(16)	10(20)	11(22)	9(18)	10(20)
104	39(78)	38(76)	41(82)	28(56)	30(60)	30(60)	30(60)	32(64)

[a]data calculated from pages 55-57 and 318-336 of registrant report.

[b]cumulative mortality (percent mortality)

The registrant stated (page 31 of report) that a total of 147 males and 133 females died or were killed during the study. In males, mortality was from the main dose group only; in females, 128 rats from the main dose group died or were killed during the study, and 5 females from the interim sacrifice group died or were killed.

No significant differences in mortality were observed between control and treated rats of either sex over the duration of treatment. However, mortality among control male rats and those in the 175ppm dose group was slightly higher than expected. The registrant stated that the slightly higher mortality could not be associated with treatment. The higher than expected incidence of mortality in control male rats deserves additional explanation from the registrant.

B. Body Weights

Rats were weighed on the date of study initiation, weekly thereafter for the next 14 weeks, bi-weekly thereafter, and again before necropsy. Group mean body weights at selected times are presented in **Table 2**.

TABLE 2

Group Mean Body Weights in Male and Female Rats Given SC-5676 in the Diet for 104 Weeks[a]

Week of Study	Males (g)				Females (g)			
	0	18	175	1750	0	18	175	1750
0	143		149	146	129	126	126	126
1	202	202	206	196	158	154	155	151
13	540	524	538	496	278	274	277	255
26	656	635	654	588	315	313	316	281
52	811	774	810	702	410	410	406	340
104	870	857	820	773	610	625	606	448

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

Body weight in male and female rats at the 1750ppm dose level was decreased relative to control rats throughout the study. The percentage decrease in absolute body weight was progressive in both sexes up to week 52. At week 104, body weight in male rats was decreased 12% vs controls, while in female rats this percentage was higher (decreased 27% vs control). Body weight in male rats at the 18ppm dose level was also decreased relative to control from week 13 of the study. This was apparently not related to treatment, as body weights in the 175ppm dose group of males were not affected.

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

TABLE 3

Group Mean Body Weight Gains in Male and Female Rats Given SC-5676 in the Diet for 104 Weeks[a]

	Males				Females			
	0	18	175	1750	0	18	175	1750
Body weight (week 0)	143	145	149	146	129	126	126	126
Weight gain (grams):								
0-13	396	379[b]	390	349[c]	150	147	151	129[c]
%control	-	96	98	88	-	98	101	86
0-52	668	629[b]	662	555[c]	281	283	279	213[c]
%control	-	94	99	83	-	101	99	76
0-104	727[d]	712[d]	671[d]	627[a,d]	481	499	479	322[c]
%control	-	98[d]	92[d]	86[d]	-	104	100	67

[a]data taken from Table 4b, pages 70-71 of registrant report.

[b]significantly different vs control ($p < 0.05$)

[c]significantly different vs control ($p < 0.001$)

[d]data recalculated from Table 4a, pages 66-69 of registrant report

As shown above, body weight gain was significantly decreased in both male and female rats in the 1750ppm dose groups, and was consistently affected throughout the study. Weight gain in male rats in the 1750ppm dose group was decreased by 12% over the 0-13 week period of the study, and in female rats was affected similarly (14% decrease). Weight gain in male rats from weeks 0-52 was decreased 17% vs control, and in female rats was affected to a slightly greater degree (decrease of 24% vs control). For the entire study period (weeks 0-104), body weight gain was decreased 14% in male rats vs control, and was decreased 33% in females vs control. Thus, effects of test article treatment at 1750ppm on body weight gain appeared slightly greater in female than male rats.

There were significant effects on body weight gain in male rats in the 18ppm dose group from weeks 0-13 (4%

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decrease vs control) and 0-52 (6% decrease vs control). These changes were statistically significant at the 0.05 level of probability, but were not likely related to treatment with test article, as no effect was observed at the next highest dose level (175ppm). However, it should be noted that overall weight gain in male rats at the 175ppm dose level was decreased 8% vs control when data were recalculated. Thus, there appears to be a dose-related trend in body weight gain decrease for both male and female rats.

C. Food Consumption and Efficiency

Food consumption was calculated for each rat on a weekly basis by measurement of the amount of food given and that remaining in the hoppers. Scattered food was estimated twice each week and included in the food residue for calculation of the food consumption. Food efficiency was calculated as the weight of food consumed per unit gain in body weight. Food efficiency was calculated for the first 14 weeks of treatment and for 13 week periods until study termination.

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

TABLE 4

Group Mean Food Consumption in Male and Female Rats Given SC-5676 in the Diet for 104 Weeks[a]

	Food consumption (g/rat/week)							
Weeks	Males				Females			
of Study	0	18	175	1750	0	18	175	1750
1-13	190	189	190	181[d]	133	133	135	128[b]
%control	-	99	100	95	-	100	101	96
1-52	186	181	183	173[d]	134	133	133	126[d]
%control	-	97	98	93	-	99	99	94
1-78	198	189[c]	190[b]	178[d]	143	140	141	132[d]
% control	-	95	96	90	-	98	99	92
1-104	204	187[c]	188[c]	177[d]	145	145	146	133[c]
%control	-	92	92	87	-	100	101	92

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[a]data from Table 3, pages 58-65 of registrant report.

[b]significantly different vs control ($p < 0.05$)

[c]significantly different vs control ($p < 0.01$)

[d]significantly different vs control ($p < 0.001$)

As shown in **Table 4**, group mean food consumption in male and female rats was affected primarily at the 1750pp dose level. Significant effects were noted in male rats continuously from weeks 0-97, and in female rats from weeks 104. From study week 0-13, food consumption was decreased by 5% in male rats vs control, and by 4% in female over this time period. From weeks 0-78, food consumption was decreased 10% overall in male rats, and 8% overall female rats. For the entire study period, food consumption was decreased 13% in male rats at the 1750ppm dose lev and 8% in female rats at this dose level.

Food efficiency (total food consumed / total weight gain) 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 SC-5676 in the Diet for 104 Weeks[a]

Weeks of Study	Food efficiency (g food/g body weight gain) Males 0	18	175	1750	Females 0	18	175	1750
1-7	4.9	5.1	5.0	5.3	9.3	9.1	9.1	10.2
7-14	13.3	13.8	13.9	15.5	34.2	29.5	27.8	44.9
1-14	9.1	9.5	9.5	10.4	21.7	19.3	18.4	27.5

[a]data recalculated from Table 5, page 72 of registrant report.

From the above recalculated data, food efficiency was apparently affected slightly in males from the 1750ppm dose group from weeks 1-14 of the study (10.4 vs 9.1). A similar effect was observed in female rats from the 1750ppm dose group, except that the magnitude of the effect appeared somewhat greater at this dose (27.5 vs 21.7). This pattern of change appeared to extend throughout the study period in both sexes, although it is to be

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noted that overall food efficiency for the study duration was unaffected in male rats at the 1750 ppm dose level vs control (29.2 vs 29.5), while in female rats food efficiency at the 1750ppm dose level was different from control (43.0 vs 31.4, page 73 of report).

The combined observations of decreased body weight gain, food consumption, and food efficiency supports the conclusion of test article toxicity. While food consumption and body weight gain decreases in male rats are closely parallel for the study duration (12% decrease in body weight, 13% decrease in food consumption), food consumption was decreased 8% in female rats for weeks 0-104 of the study, but body weight gain was decreased 33%, as reflected in the overall decreased food efficiency in female rats, both for weeks 1-14 and for the study duration. Thus, treatment with test article at 1750ppm may be more toxic to female rats as shown by these data.

D. **Intake of SC-5676**

The group mean intake of SC-5676 for male and female rats over the course of the study is summarized in the following table (**Table 6**):

TABLE 6

Group Mean Achieved Dosage of SC-5676 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
18	0.9	0.67	0.88
175	8.75	6.37	8.53
1750	87.5	66.9	92.1

[a]data taken from Table 6, page 77 of registrant report.

Achieved dosage of SC-5676 was based upon concentration of the active ingredient in dietary formulations (91%). Thus, the actual nominal dose levels received by rats in this study were **0, 16, 159, and 1589 ppm** (0, 0.8, 7.96, and 79.6 mg/kg/day). Group mean achieved intake of SC-5676 was between 80-84% of nominal for male rats in all dose groups, while an achieved intake of between 107-115% was calculated in female rats in all dose groups.

Note: The approximately 20% difference in achieved intake of SC-5676 between male and female rats could explain in part the apparently greater effects of test article on female rats at the 1750ppm dose level.

E. Ophthalmoscopic Examination

Both eyes of all rats were examined prior to initiation of the study by means of a Fisons Binocular Indirect Ophthalmoscope after instillation of 0.5% tropicaimide. Nine males and 12 females with relatively severe ocular abnormalities were discarded prior to the study and replaced with spare animals bearing no abnormalities. During the course of treatment, surviving rats were examined at week 23, 49, 76, and 101. An additional examination was performed on all surviving males after 97 weeks of treatment.

As stated by the registrant (page 29 of report), observations of hyaloid remnants and persistent hyaloid arteries were omitted from the results as they were considered normal developmental structures and there was no indication of a treatment related disturbance.

Ophthalmic examination after 76 weeks of treatment revealed a high proportion (24 of 43 rats, 55%) of female rats in the 1750ppm dose group with hyperreflection ($p < 0.001$ vs controls). This ocular lesion was also present in female rats at 101 weeks (15 of 25 rats, 60%; $p < 0.05$ vs control). In the majority of affected female rats this lesion was bilateral. The incidence of this lesion in female rats at the 18 and 175ppm dose levels was not significantly different from control values.

In male rats at the 1750ppm dose level, foci or plaques in the vitreous or on the posterior capsule of the lens (page 32, section 5.7 of report) were observed in increased incidence beginning at 76 weeks, and were observed in increased incidence in this dose group at subsequent examination times. At 76 weeks, 12 of 42 male rats in the 1750ppm dose group (28%; $p < 0.05$ vs control) were observed with this lesion, and 10 of 26 remaining rats (38%) were observed with this lesion at 97 weeks. At 101 weeks, 9 of 25 remaining rats (36%) were observed with this lesion. In most cases, this lesion was bilateral. Male rats at the other dose levels were not observed with an increased incidence of this lesion when compared to control values.

With the exception of those lesions described above, no other ocular lesions were attributed to administration of SC-5676 at any dose level in either male or female rats.

F. Clinical Signs and Pathology

Examination of rats for any sign of ill health or systemic toxicity was recorded twice daily. Examination for palpable masses was made once a week. The location, size, consistency, time of first observation and subsequent course were noted for each palpable mass.

Blood samples were obtained from the orbital sinus of 20 male and 20 female rats with the highest identity numbers from each dose group. Blood was withdrawn at weeks 13, 24, 50, 78, and 102 under light ether anesthesia following an overnight fast.

Collected blood was mixed with EDTA anticoagulant for hematological examination, and with heparin anticoagulant for biochemical measurements. An Ortho ELT-8ds automated hematology analyzer was utilized for hematology measurements.

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a) **Hematology**

The following CHECKED hematological parameters were examined:

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

*EPA guideline requirement "-" not analyzed

13 weeks

Male rats in the 1750 ppm dose group showed an increased total white blood cell count vs control (17.8 vs 15.4 1000 cells/cm^2, $p < 0.05$). However, no such effect was observed at the 1750ppm dose level. Female rats in the 1750ppm dose group showed decreases in platelet counts (579 vs 627 1000/cm^2 in control, $p < 0.05$) packed cell volume (45 vs 47% in control, $p < 0.05$), and an increase in mean corpuscular hemoglobin concentration 35 vs 34%, $p < 0.01$ vs control).

24 weeks

Hemoglobin concentration in male rats was significantly ($p < 0.05$) increased at the 18ppm dose level vs control, as was red blood cell number (8.93 vs 8.65 mil/cmm). Platelet number was observed to be low at the 175 and 1750ppm dose level (565 and 591 vs 647 1000/cmm); however, the control value had a high standard deviation (103) which was due to 2 abnormally high values. Thus, the intergroup differences observed at 175 and 1750ppm were not considered treatment related.

No significant hematological effects were observed in female rats at 24 weeks.

50 weeks

No significant hematologic effects were observed.

78 weeks

In male rats, no significant effects were observed.

In female rats, an increase in platelet count was observed at the 18ppm dose level vs control (638 vs 573 1000/cmm).

102 weeks

In male rats, mean corpuscular volume in the 1750ppm dose group was significantly ($p < 0.05$) decreased vs control (53 vs 57%). No other changes were reported as significant.

In female rats, mean corpuscular hemoglobin concentration was significantly increased at all doses vs control, and mean corpuscular volume was significantly ($p < 0.001$) decreased in the 1750ppm dose group vs control (56 vs 62cμ).

The registrant stated (page 33) that abnormally low erythrocyte characteristics (packed cell volumes, hemoglobin concentration, and erythrocyte counts) were reported after 50, 78, and 102 weeks of treatment, especially in males. While low but non-statistically significant values for these parameters were observed in male rats at 50 weeks in the 175 and 1750ppm dose groups, such a trend was not apparent at 78 or 102 weeks upon inspection of the data (Table 8c-8 pages 97-102 of report).

Note: In the subchronic toxicity study with acetochlor in rats (MRID# 415920-04), an apparent dose-related trend towards increased hemoglobin levels and decreased platelet levels in male rats was observed at 12 weeks, as was an increase in red blood cells in female rats. These changes were significant at the highest dose in this study (2000ppm). However, such changes are not apparent at 13 weeks in the present study.

b) **Clinical Chemistry:**

Blood samples were obtained for blood chemistry measurements at week 24, 50, 78 and 102 under the same conditions governing the sampling of blood for hematological analysis, except that lithium heparin was used as the anticoagulant. The following CHECKED parameters were measured:

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

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

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

*EPA guideline requirement "-" not examined

Note: Measurement of albumin as recommended by the guidelines (83-5) was replaced by measurment of electrophoretic protein fractions.

Significant findings in blood chemistry measurements are summarized below for male and female rats (Table 7):

Table 7

Blood Chemistry in Male and Female Rats Administered SC-5676 in the Diet for 104 Weeks[a]

	Males				Females			
	0	18	175	1750	0	18	175	1750
24 Weeks								
GGT (iu/l)	2±1	2±1	2±1	4±1[b]	3±1	3±1	3±1	4±1
cholesterol (mg%)	77±27	83±18	88±17	91±10	99±10	99±21	92±26	105±23
50 Weeks								
GGT (iu/l)	2±1	1±2	1±1	3±2[b]	1±1	1±1	0±0	1±1
cholesterol (mg%)	85±31	80±22	84±23	90±27	90±33	98±21	86±26	106±36
AST(iu/l)	58±9	70±13[b]	67±16	72±13[b]	71±17	62±8	69±15	71±27
78 Weeks								
GGT (iu/l)	4±3	2±1	5±6	8±6[b]	0±0	0±1	0±0	0±1
cholesterol (mg%)	113±53	133±44	137±45	132±42	120±22	119±31	131±34	144±28
102 Weeks								
GGT (iu/l)	5±2	6±3	5±2	8±3[b]	2±1	3±2	2±1	3±2[b]
cholesterol (mg%)	115±20	149±82	136±57	180±67[b]	147±52	167±96	150±97	141±34

[a]data taken from Tables 9a-9d, pages 103-119 of report.

[b]significantly different vs controls, $p < 0.05$.

As summarized above, consistent and significant increases in GGT were observed in male rats in the 1750ppm dose group throughout the study. Blood cholesterol showed a similar trend, although the increase at 1750ppm was significant only at week 102.

In female rats, GGT was significantly increased in the 1750ppm dose group only at week 102, while blood cholesterol showed an apparent dose related increase up to week 78. However, this increase was not statistically significant over the course of the study for female rats.

c) **Urinalysis:**

Overnight urine samples were collected from the 10 males and females used for hematological analysis and blood chemistry when possible after 11, 23, 49, 77, and 101 weeks of treatment. Urine was collected from rats placed in individual metabolism cages under conditions of food and water deprivation (16 hours).

The following CHECKED parameters were examined:

_x_ 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

Note: Group mean values for urine volume, pH, and specific gravity are given in Tables 10a-10e, pages 119-123 of the registrant's report; values for the remaining urine parameters are found in Appendix 10a-10e, pages 964-983 of the report.

No apparent test article related effects on measured urinary parameters were reported during the course of this study.

G. **Macroscopic Observations** (Table 12a-12d, pages 132-163)

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.

Detailed examination of external features and orifices was made at necropsy, as well as examination of the neck and associated tissues, the cranial, thoracic, abdominal, and pelvic cavities and associated viscera, and the carcass. Abnormalities, interactions, and changes were recorded and tissues were preserved in fixative.

No treatment related macroscopic lesions were apparent either among those rats killed or dying during the

treatment period, or among those killed at 52 and 104 weeks of treatment.

H. **Organ Weights** (Tables 11a-11d, pages 124-131 of report).

Organs to be weighed were obtained from all animals dying or killed during the study and dissected free of fat and contiguous tissue before weighing. The following organs were weighed: adrenals, brain, heart, kidneys, liver, testes, and ovaries, prostate. Group mean and individual organ weights were provided. Organ/body weight ratios were also provided.

Absolute organ weights were unaffected at 52 weeks of treatment, as shown by the registrant in Tables 11a, pages 124-125 of the report. Organ:body weight ratios, however (Table 11b, pages 126-127 of report), were significantly affected for the brain, heart, kidneys, and liver of female rats at the 1750ppm dose level, and for the kidneys and [illegible]nale rats at this dose level. Results are summarized below (Table 8):

Table 8

Organ:Body Weight Ratios at 52 Weeks in Male and Female Rats Administered SC-5676 in the Diet[a]

	Males				Females			
	0	18	175	1750	0	18	175	1750
brain	0.29±0.03	0.29±0.03	0.27±0.03	0.3±0.02	0.48±0.07	0.47±0.09	0.52±0.09	0.58±0.11[c]
heart	0.23±0.02	0.23±0.03	0.22±0.01	0.25±0.04	0.28±0.03	0.28±0.03	0.3±0.03	0.33±0.07[c]
kidneys	0.62±0.05	0.61±0.07	0.62±0.04	0.69±0.06[c]	0.67±0.1	0.65±0.11	0.71±0.08	0.82±0.09[d]
liver	3.19±0.7	3.16±0.28	3.30±0.24	3.56±0.4[b]	3.51±0.4	3.45±0.54	3.52±0.3	3.92±0.46[c]

[a]data taken from Table 11b, pages 126-127 of report.

[b]$p < 0.05$ vs control; [c]$p < 0.01$ vs control; [d]$p < 0.001$ vs control.

Absolute organ weights at terminal sacrifice (Table 11c, pages 128-129 of report) were not significantly altered in male rats except adrenal weight at the 1750ppm dose level, which decreased from 0.125±0.03g to 0.097±0.044g. In female rats, significant decreases in brain weight (1.92±0.1 vs 1.99±0.09g), heart weight (1.35±0.19 vs 1.61±0.27g), and liver weight (17.0±3.5 vs 20.1±4.1g) were observed at the 1750ppm dose

level.

Organ:body weight ratios were unaffected at 104 weeks except in the brain of female rats at the 1750ppm dose level, where the brain:body weight ratio increased from 0.34±0.06 in controls to 0.44±0.08 in the 1750ppm dose group.

I. Microscopic Observations

Samples of the following tissues were preserved in either 4% buffered formalin (all tissues except eyes) or Davidson's fixative (eyes and optic nerve). All macroscopically abnormal tissues were also preserved along with samples of normal tissue where appropriate.

Digestive

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

Respiratory

_x_ trachea
_x_ lungs*
_x_ nasal cavity

Cardiovascular

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

Urogenital

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

Neurologic

_x_ brain*
_x_ peripheral nerve*
_x_ spinal cord (3 levels)*
_x_ pituitary*
_x_ eyes

Glandular

_x_ adrenals *
_x_ lacrimal gland
_x_ mammary gland
_x_ parathyroids*
_x_ thyroids*

Other

_x_ bone (femur)
_x_ skeletal
_x_ muscle
_x_ skin*
_x_ all gross lesions*

*EPA guideline requirement

"-" not examined

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Tissues were prepared for microscopic examination by embedding in paraffin wax, cutting thin sections (5μm), and staining with hematoxylin and eosin. Microscopic examination was performed on the above tissues from all rats in control and high dose groups sacrificed at 52 weeks, on all rats killed at 104 weeks, and on all decedent rats.

1a) Neoplastic and Non-Neoplastic Observations-52 Weeks (Interim Sacrifice Group)

Two female rats in the control group and 3 female rats in the 1750ppm dose group assigned to the 52 week sacrifice died before sacrifice. In these rats, there was no apparent effect of test article on tumor formation (Table 13A, page 164 of report). In those rats surviving the 52 week treatment period (Tables 13E and 13F, pages 193-202 of the report), increased incidences of nasal epithelial adenomas and nasal epithelial hyperplasia in both male and female rats at the 1750ppm dose level were observed, as summarized below (Table 9):

TABLE 9

Incidence of Neoplastic and Non-Neoplastic Lesions in Surviving Male and Female Rats Given Dietary SC-5676 for 52 Weeks (Interim Sacrifice Group)[a]

	Males				Females			
Dose (ppm)	0	18	175	1750	0	18	175	1750
Head								
No. of Animals Examined	20	10	10	20	18	9	10	16
Adenoma of Nasal Epithelium	0[b] (0)[c]	0 (0)	0 (0)	5 (25)[d]	0 (0)	0 (0)	0 (0)	8 (50)[f]
Hyperplasia of Nasal Epithelium	0 (0)	0 (0)	0 (0)	11 (55)[f]	0(0)	0(0)	0(0)	13(76)[f]

[a]data taken from Table13E and 13F, pages 193-202 of registrant report.

[b]number of rats with specified lesion.

[c]percentage of rats with specified lesion.

[d]$p < 0.05$ vs control; [f]$p < 0.001$ vs control

As shown in **Table 9**, male and female rats at the 1750ppm dose level showed a significant increase in the incidence of nasal epithelial adenomas and nasal epithelial hyperplasia after 52 weeks of treatment. No other treatment related lesions at 52 weeks were reported.

1b) Neoplastic and Non-Neoplastic Observations-104 Weeks (Terminal Sacrifice Group)

i. Rats Assigned to 104 Weeks of Treatment Dying or Killed During the 104 Week Treatment Period (Tables 13C and 13D, pages 168-192 of the report)

Adenoma of the nasal epithelium was observed in those rats dying or killed which had been assigned to the 104 week treatment period. This occurred solely in the 1750ppm dose group. In males, 17 of the 28 rats (60%)which died or were killed were found with this tumor type, while 18 of 31 female rats which died or were killed (58%) were found with this tumor type. Carcinoma of the nasal epithelium was observed in 1 female rat at the 1750ppm dose level.

Benign chondroma of the femur was observed in 1 male rat from the 1750ppm dose group, as was benign basal cell tumor of the stomach in 1 male and 1 female from the 1750ppm dose group (Table 13C, pages 168-171 of report).

Non-neoplastic observations in those rats dying or killed during the 104 week treatment period included hyperplasia of the nasal epithelium (solely at the 1750ppm dose level in both sexes), purulent rhinitis (males only at the 1750ppm dose level), squamous metaplasia of the olfactory epithelium (males only at the 1750ppm dose level), pelvic epithelial hyperplasia in the kidney (dose related trend in both males and females), degeneration of the retinal outer nuclear layer in the eye (females in the 1750ppm dose group only), fatty infiltration of the pancreatic stroma (females in the 1750ppm dose group), and parafollicular hyperplasia of the cervical lymph nodes (dose-related trend in male rats). These findings are summarized below (Table 10):

TABLE 10

Incidence of Non-Neoplastic Lesions in Decedent Male and Female Rats Given Dietary SC-5676 for 104 Weeks[a]

	Males				Females			
Dose (ppm)	0	18	175	1750	0	18	175	1750
No. Animals Examined	40	37	41	28	30	31	34	31
Hyperplasia of Nasal Epithelium	0[b](0)[c]	0(0)	0(0)	17(60)[e]	0(0)	0(0)	0(0)	17(54)[e]
Purulent Rhinitis	0(0)	1(3)	3(7)	4(14)[d]	1(3)	1(3)	2(6)	1(3)
Metaplasia-Olfactory Epithelium	0(0)	0(0)	0(0)	4(14)[d]	0(0)	0(0)	1(3)	0(0)
Kidney								
No. animals examined	40	38	41	28	30	31	35	31
pelvic epithelial hyperplasia	5(12)	6(16)	9(22)	15(53)[e]	2(7)	4(13)	7(20)	8(26)
Eye								
No. animals examined	38	31	37	27	29	29	33	27
retinal outer nuclear layer degeneration	0(0)	0(0)	1(3)	3(11)	2(7)	2(7)	7(21)	11(40)[d]

Table 10, cont.

	Males				Females			
Dose (ppm)	0	18	175	1750	0	18	175	1750
Pancreas								
No. animals examined	40	37	41	27	30	31	35	31
stromal fatty infiltration	9(22)	6(16)	5(12)	2(7)	4(13)	7(22)	12(34)	13(42)[d]
Cervical lymph node								
No. animals examined	39	37	40	27	30	31	35	31
parafollicular hyperplasia	4(10)	5(13)	6(15)	9(33)[d]	1(3)	4(13)	6(17)	4(13)

[a]data taken from Table 13D, pages 172-192 of report.

[b]number of animals with specified lesion; [c]percent of animals with specified lesion

[d] $p < 0.05$ vs control; [e]$p < 0.001$ vs control.

As shown above, hyperplasia of the nasal epithelium was observed solely at the 1750ppm dose level in both sexes, while purulent rhinitis and metaplasia of the olfactory epithelium affected male rats only at the 1750ppm dose level. In contrast to these effects, pelvic hyperplasia of the kidney showed an apparent dose-related increase in both male and female rats, which was statistically significant only in male rats, although the incidence of this lesion increased from 7% in control females to 26% in 1750ppm dose group females.

Non-neoplastic lesions related to treatment with SC-5676 confined primarily to female rats included retinal outer nuclear layer degeneration (increased from 7% in controls to 40% at the 1750ppm dose level) and stromal fatty infiltration of the pancreas (increased from 13% in controls to 42% at the 1750ppm dose level). Parafollicular hyperplasia of cervical lymph nodes showed an apparent dose related increase in male rats, increasing from 10% in controls to 33% at the 1750ppm dose level.

Other changes stated by the registrant (page 36) included 2 cases of glandular hyperplasia with dystrophy and giant cell formation in the stomach of male rats from the 1750ppm dose group (reported as a rare finding), and a

D

higher incidence of females in the 1750ppm dose group which were in proestrous as evidenced by vaginal changes (page 186 of report).

ii. Rats Surviving the 104 Week Treatment Period (Terminal Sacrifice Group)

Neoplastic observations reported in rats which survivied the 104 week treatment period were confined to a significant increase in adenoma of the nasal epithelium of male and female rats at the 1750ppm dose level, the presence of a benign chondroma of the femur in 1 female rat at the 1750ppm dose level, and carcinoma of the nasal epithelium in 2 male rats from the 1750ppm dose group. Data are summarized by the registrant in Table 13G, pages 203-205 of the report, and are summarized in Table 11 below:

TABLE 11

Incidence of Neoplastic Lesions in Surviving Male and Female Rats Given Dietary SC-5676 for 104 Weeks (Terminal Sacrifice Group) [a]

	Males				Females			
Dose (ppm)	0	18	175	1750	0	18	175	1750
No. animals examined:	10	12	9	22	20	19	15	18
Adenoma of Nasal Epithelium	0[b] (0)[c]	0(0)	0(0)	13(59)[d]	0(0)	0(0)	0(0)	10(55)[e]
Carcinoma of Nasal Epithelium	0(0)	0(0)	0(0)	2(15)	0(0)	0(0)	0(0)	0(0)

[a] data from Table 13G, pages 203-205 of registrant report.

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

[d] $p < 0.01$ vs control; [e] $p < 0.001$ vs control

Non-neoplastic findings in those rats surviving the 104 week treatment period are summarized by the reigistrant in Table 13H, pages 208-219 of the report, and also below (Table 12):

TABLE 12

Incidence of Non-Neoplastic Lesions in Surviving Male and Female Rats Given Dietary SC-5676 for 104 Weeks (Terminal Sacrifice Group)[a]

	Males				Females			
Dose (ppm)	0	18	175	1750	0	18	175	1750
No. animals examined:	10	12	9	22	20	19	15	18
Hyperplasia of Nasal Epithelium	0[b] (0)[c]	0(0)	0(0)	8(36)	0(0)	0(0)	0(0)	11(61)[f]
Adrenal Cortex-focal hyperplasia	4(40)	6(50)	4(44)	7(32)	6(30)	3(15)	6(40)	12(66)[d]
Adrenal Medulla-hyperplasia	2(20)	6(50)	1(11)	16(72)	1(5)	0(0)	3(20)	4(22)
Pancreas-stromal fatty infiltration	0(0)	5(41)[d]	3(33)	13(59)[e]	11(55)	12(63)	8(53)	10(55)

[a] data from Table 13H, pages 206-219 of registrant report.

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

[d] $p < 0.05$ vs control; [e] $p < 0.01$ vs control; [f] $p < 0.001$ vs control.

The only lesions considered treatment related by the registrant included the significantly increased incidence of hyperplasia of the nasal epithelium in females from the 1750ppm dose group, and the increased incidence of stromal fatty infiltration of the pancreas in male rats from the 18 and 1750ppm dose groups. Increased incidence of focal cortical hyperplasia of the adrenal cortex in females from the 1750ppm dose group and increased incidence of hyperplasia of the adrenal medulla in male rats from the 1750ppm dose group were also observed as non-neoplastic lesions in surviving rats. While hyperplasia of the adrenal cortex was felt to be unrelated to treatment as stated on page 37 of the registrant's report, it was unclear whether hyperplasia of the adrenal medulla was also meant to be included, as this followed a similar pattern of incidence with dose.

A lower incidence of female rats in diestrus at the 1750ppm dose level was observed in relation to controls. This observation is supportive of evidence in females from the 52 week time point of the study in which a higher incidence of females in proestrus was observed at this same dose level, and suggests some type of test article

interference with the reproductive physiology of female rats.

iii. Neoplastic Observations Combined-104 Weeks

Combined neoplastic findings in decedent **and** surviving rats from 104 weeks of treatment is presented below (Table 13):

TABLE 13

Incidence of Neoplastic Lesions in Male and Female Rats Given Dietary SC-5676 for 104 Weeks (Terminal Sacrifice Group: Decedent + Surviving)[a]

	Males				Females			
Dose (ppm)	0	18	175	1750	0	18	175	1750
No. animals examined:	50	49	50	50	50	50	49	49
Adenoma of Nasal Epithelium	0[b] (0)[c]	0(0)	0(0)	30(60)[e]	0(0)	0(0)	0(0)	28(57)[e]
Carcinoma of Nasal Epithelium	0 (0)	0(0)	0(0)	2(4)	0 (0)	0(0)	0(0)	1(2)
Thyroid- No. animals examined	50	50	48	50	50	50	50	49
follicular cell adenoma	2(4)	1(2)	2(4)	5(10)	1(2)	1(2)	3(6)	5(10)

[a]data from Table 13I, pages 220-224 of registrant report.

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

[d] $p < 0.05$ vs control; [e] $p < 0.01$ vs control; [f] $p < 0.001$ vs control.

As shown, a significant increase in adenomas of the nasal epithelium was observed in both male and female rats at the 1750ppm dose level. This increased in nasal epithelial adenomas was also significant when decedent (see section [1b], page 19 of DER) and surviving rats were considered separately, supporting the treatment related

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nature of the effect. The finding of follicular cell adenomas of the thyroid was apparently treatment related only when decedent and surviving rats were combined. The trend of this increase was significant for female rats as analyzed by the Cochran-Armitage test ($p < 0.05$, page 38 of registrant report), but was not statistically significant for male rats, even though the percentage of rats with this tumor was equivalent between sexes at the 1750ppm dose level (10%). The incidence of thyroid follicular cell adenoma at the 1750ppm dose level in females was outside the historical control range for this tumor type (see historical control data attached to this DER).
A summary of non-neoplastic findings in decedent and surviving rats from 104 weeks of treatment follows (Table 14):

TABLE 14

Incidence of Non-Neoplastic Lesions in Male and Female Rats Given Dietary SC-5676 for 104 Weeks (Terminal Sacrifice Group: Decedent + Surviving)[a]

	Males				Females			
Dose (ppm)	0	18	175	1750	0	18	175	1750
No. animals examined:	50	50	50	50	50	50	50	49
Adrenal Cortex-								
focal hyperplasia	9[b](18)[c]	19(38)[d]	12(24)	11(22)	11(22)	9(18)	14(28)	21(42)[d]
Retina-								
No. animals examined	48	43	46	49	49	48	48	45
degeneration of								
outer nuclear layer	2(4)	1(2)	2(4)	7(14)	13(26)	7(14)	14(28)	24(48)[d]
Nasal Epithelium								
No. animals examined	50	49	50	50	50	50	49	49
hyperplasia	0 (0)	0(0)	0(0)	25(50)[f]	0(0)	0(0)	0(0)	28(57)[f]
Kidney-								
No. animals examined	50	50	50	50	50	50	50	49
pelvic epithelial								
hyperplasia	6(12)	7(14)	10(20)	22(44)[f]	4(8)	7(14)	9(18)	14(28)[e]

Table 14, cont.

	Males				Females			
Dose (ppm)	0	18	175	1750	0	18	175	1750
Pancreas-								
No. animals examined	50	49	50	49	50	50	50	49
stromal fatty infiltration	9(18)	11(22)	8(16)	15(30)	15(30)	19(38)	20(40)	23(47)

[a]data from Table 13J, pages 225-247 of registrant report.

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

[d] $p < 0.05$ vs control; [e] $p < 0.01$ vs control; [f] $p < 0.001$ vs control.

As shown previously for rats considered separately at 104 weeks as either surviving (Table 12) or decedent (Table 10), significant increases in the incidence of nasal epithelial hyperplasia, kidney pelvic epithelial hyperplasia, and degeneration of the outer retinal nuclear layer were seen in either male or female rats at the 1750ppm dose level. Stromal fatty infiltration of the pancreas was not significantly increased at the 1750ppm dose level, but showed an apparent trend for an increase in both male and female rats with increasing dose of test article.

The most significant neoplastic observation in response to administration of test article was adenoma and carcinoma of the nasal epithelium, while hyperplasia of the nasal epithelium was most significantly affected in reponse to administration of test article.

It should be noted that upon inspection of individual animal data (Appendix 12B, pages 1468-1568 and 1855-1954; Appendix 12D, pages 2215-2284 and 2434-2490), the presence of nasal epithelial hyperplasia and adenomas occurred together in 13 male rats at the 1750ppm dose, and in 14 female rats at the same dose level. Multiple nasal adenomas were observed in 11 male rats at the 1750ppm dose level, and in 9 female rats at this dose level. The presence of nasal hemorrhage was evident in 6 male rats at the 1750ppm dose level, and in 2 female rats at this dose.

III. DISCUSSION

In the present study, male and female Sprague-Dawley rats were administered SC-5676 technical in the diet for 104 weeks at levels of 0, 18, 175, and 1750 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 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. Effects of test article treatment on neoplastic and non-neoplastic responses in decedent rats and those sacrificed at study termination was delineated, as was the effect of test article treatment on these responses in the combined groups.

Mortality was not significantly altered in test article treated rats of either sex in comparison to control rats. Mortality in control male rats, was, however, slightly higher over the course of the study (78%) than usual. No explanation was given by the registrant as to why this occurred.

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. Absolute body weight at 13 weeks was decreased in both male and female rats in the 1750ppm dose group by 9%. At 52 weeks of the study, this decrease was 14% and 18% for males and females, respectively. Overall absolute body weight was decreased 12% in males and 27% in females for weeks 0-104 of the study.

Body weight gain was also affected throughout the study, primarily in male and female rats from the 1750ppm dose group. Weight gain for weeks 0-13 was decreased 12% in male rats at the 1750ppm dose level, and was decreased 14% in female rats at this dose level. At week 52 of the study, body weight gain in male and female rats from the 1750ppm dose level was decreased 17% and 24%, respectively. Overall body weight gain for male and female rats at the 1750ppm dose level was decreased 14% and 33%, respectively, in comparison to controls. Thus, the effects of test article treatment on body weight and body weight gain were most apparent at the 1750ppm dose level.

The decrease in body weight gain for male and female rats at the 1750ppm dose levels during the first 13 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 also affected during this time period, primarily at the 1750ppm dose level. The combined observations of decreased body weight gain, food consumption, and food efficiency supports the conclusion of test article toxicity. While food consumption and body weight gain decreases in male rats were closely parallel for the study duration (12% decrease in body weight, 13% decrease in food consumption), food consumption was decreased 8% in female rats for weeks 0-104 of the study, but body weight gain was decreased 33%, as reflected in the overall decreased food efficiency in female rats, both for weeks 1-14 and for the study duration. Efficiency of food conversion was less affected by test article treatment in male rats.

Ophthalmologic effects from administration of test article were evident in both male and female rats in the 1750ppm dose level beginning at week 76. In male rats, this lesion consisted of foci or plaques in the vitreous or on the posterior capsule of the lens, and was often observed bilaterally. No apparent histopathological lesion was

asssociated with this ocular alteration. In females, the primary ocular change observed was hyperreflection of the ocular fundus. According to the registrant (page 39), this observation is often associated with a reduced thickness of the retinal layer and is supported by the histopathological observation of degeneration of the retinal outer layer. Thus, significant ocular effects from test article administration were observed in both male and female rats at the 1750ppm dose level.

Some hematological parameters were altered at each time point of examination during the study, such as platelet counts, mean corpuscular hemoglobin concentration, and packed cell volume. However, these effects were not consistent over time and did not display a dose related trend in most cases. The relative lack of hematologic effects in this study is supported by previous results from subchronic administration of SC-5676 to male and female rats, where a trend towards increased hemoglobin levels and decreased platelets was observed in male rats, and increases in red blood cells were observed in female rats after 13 weeks. These results were achieved with an oral dose of 2000ppm test article. Thus, the highest dose used in this study, 1750ppm, was apparently not high enough to produce significant hematologic effects as those produced in the subchronic study with SC-5676. It is apparent that SC-5676 would cause hematologic effects at high enough doses.

Most clinical blood chemistry parameters were unaffected over the course of treatment with SC-5676. However, a consistent increase in gamma-glutamyl transpeptidase (GGT) was observed in male rats at the 1750ppm dose level, as was a consistent increase in blood cholesterol at this dose. Similar changes were observed in female rats, but did not reach statistical significance at the 1750ppm dose level, except for GGT at 102 weeks. A dose-related trend for increased blood cholesterol was also observed in the subchronic rat study with SC-5676, but no changes in GGT were observed.

Analysis of urine during the study did not reveal any significant changes in any parameter measured in either male or female rats.

Treatment related effects on observed macroscopic lesions were also not apparent over the course of the study.

Significant effects of test article administration on absolute organ weights were not apparent at 52 weeks of treatment. However, organ:body weight ratios for the brain, heart, liver, and kidneys were significantly increased in male rats at the 1750ppm dose level, and were significantly increased in female rats at this dose level for the kidneys and liver. As with many other effects noted in this study, the significant effects occurred primarily at the 1750ppm dose level.

Nasal epithelial hyperplasia, adenoma, and carcinoma were the most significant non-neoplastic and neoplastic observations resulting from administration of SC-5676. Hyperplasia and nasal adenoma were present in both male and female rats from the 1750ppm dose level at 52 weeks. This effect was seen only at the 1750ppm dose level. These same effects were seen again in decedent and surviving rats assigned to the 104 week treatment groups, with the same finding that nasal effects were limited to the 1750ppm dose level. When decedent and surviving rats treated for 104 weeks were combined, a total of 60% of males and 57% of females in the 1750ppm dose group were found with nasal adenoma. Four percent of males and 2% of females were found with nasal carcinoma at the 1750ppm dose level. Follicular cell adenoma of the thyroid was also a significant neoplastic response in both male and female rats. Ten percent of both male and female rats from the 1750ppm dose level were found with this tumor type at 104 weeks when decedent and surviving rats were combined. A significant dose-related trend was found in female rats for this tumor, but not in males. That thyroid follicular cell adenoma

was related to treatment was supported by historical control data provided by the registrant (page 40 of report and attached Table), where the highest incidence of this tumor was found to be 6%, below the 10% incidence found in this study.

Two rare tumor types were also observed in this study. Benign chondroma of the femur was found in 1 male rat which died during the study and in 1 female rat surviving to week 104. Basal cell tumors of the stomach were also found in 1 male and 1 female rat which died during the study. The rarity of these tumor types supports the finding that these were related to administration of test material.

Treatment of male and female rats with SC-5676, especially at the 1750ppm dose level, was also apparently responsible for increases in the incidence of a number of non-neoplastic lesions in both sexes. These included epithelial hyperplasia of the kidney pelvis (increased from 6% in control males to 22% in 1750ppm males), nasal epithelial hyperplasia (increased from 0% in control males and females to 8% and 11% in 1750ppm males and females, respectively), and stromal fatty infiltration of the pancreas (increased from 9% to 15% in 1750ppm males, and from 15% to 25% in 1750ppm females). The non-neoplastic lesions of focal hyperplasia of the adrenal cortex and degeneration of the outer nuclear layer of the retina appeared to affect females in the 1750ppm dose group primarily.

The highest dose of test article examined in this study was 1750 ppm in both male and female rats. This dose caused a body weight decrement of approximately 12-14% during the first 13 weeks of treatment in both sexes of rats. This weight gain decrement persisted throughout the study in both sexes. In addition, decreased food efficiency, ophthalmoscopic abnormalities, clinical effects on GGT and cholesterol, and increased organ:body weight ratios were also observed in both sexes at 1750ppm test article. In light of these systemic effects, the 1750ppm dose level is considered a maximum tolerated dose (MTD) for the test article in this study.

IV. CONCLUSIONS

Technical SC-5676 was administered to male and female rats in the diet for 104 weeks at doses of 0, 18, 175, and 1750 ppm (0, 0.8, 7.9, and 79.6 mg/kg/day active ingredient). In males and females, systemic toxicity in the form of reduced body weight gain, decreased food efficiency, opthalmologic abnormalities, elevated GGT and cholesterol, and increased organ:body weight ratios were evident at the 1750ppm dose level, establishing this as a maximum tolerated dose for the study. Tumorigenic responses were observed in both sexes from administration of 1750ppm SC-5676. These included a significant increase in the incidence of nasal epithelial adenomas and thyroid follicular cell adenomas. Nasal carcinomas were observed in a total of 3 rats (2 males and 1 female). Rare tumors in the form of chondroma of the femur and basal cell tumors of the stomach were also observed. Non-neoplastic histopathology in the kidney, retina, pancreas, and nasal epithelium was also increased at the 1750ppm dose level.

The data in this study support the conclusion of limited evidence of carcinogenicity for technical SC-5676, based upon the occurrence of increased incidence of benign thyroid follicular cell tumors and benign and malignant nasal tumors only in high dose male and female rats , and the occurrence of benign chondroma and basal cell tumors in male and female rats.

The No Observed Effect Level (NOEL) = 175 ppm

The Lowest Observed Effect Level (LEL) = 1750 ppm (males and females; decreased body weight gain, decreased food efficiency, increased organ:body weight ratios, increased plasma GGT and cholesterol)

The Maximum Tolerated Dose (MTD) = 1750 ppm (males and females; decreased body weight gain).

V. CLASSIFICATION

Core Minimum

This study satisfies the guideline requirements (83-5) for a combined carcinogenicity/ chronic toxicity study in rats.

4.5.13 Statistical evaluation

Tests for the significance of difference between each treatment group and the corresponding controls were conducted as follows:

For bodyweight gain, food consumption, haematology, blood chemistry, urinalysis and organ weight data, a series of Student's t-tests was performed using a pooled within-group error variance. The least significant difference was calculated at the 0.1%, 1% and 5% levels of significance. Statistical significances for eosinophil, basophil and monocyte count are not reported as these data are not normally distributed.

For macroscopic and microscopic changes, inter-group differences in incidences were evaluated by Fisher's Exact Test (two-tailed for macroscopic and non-neoplastic findings, one-tailed for neoplastic microscopic findings). Tarone's extension of Cox's test (Biometrika, 62, 679-684, 1975) was used to examine linear trend on dose and to assess deviation for linearity.

Time-to-event analysis of mortality was by Cox's test, applied as an overall test for homogeneity of survival curves and for pair-wise comparison against control.

Cochran-Armitage trend test was applied to the incidences of neoplastic and non-neoplastic findings for animals allocated for terminal study.

4.6 Raw data

All raw data and specimens pertaining to this study, except those used or generated in the course of any supplier's or sponsor's analysis, are stored in the archives of Life Science Research.

Text Table 1

Historical data for control animals

Study		CDR39(1)		CDR39(2)		CDR40		CDR41(1)		CDR41(2)	
		M	F	M	F	M	F	M	F	M	F
No. examined :		50	50	50	50	50	50	50	50	50	50
Thyroid											
Follicular adenoma	No.	2	3	2	1	3	0	1	3	3	0
	%	4	2	4	2	6	0	2	6	6	0
Follicular carcinoma	No.	0	1	0	0	1	0	0	0	0	0
	%	0	2	0	0	2	0	0	0	0	0