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Attachment C

Primary Review by: Patricia A. Turck, M.S. 7/16/91
Review Section I, Toxicology Branch II (H7509C)
Secondary Review by: Yiannakis M. Ioannou, Ph.D. 7/16/91
Review Section I, Toxicology Branch II (H7509C)

008478

DATA EVALUATION REPORT

STUDY TYPE: Oncogenicity §83.2

MRID NO.: 415651-19 TOX. CHEM. NO.: 003B HED PROJECT NO.: 0-1999

TEST MATERIAL: SC-5676

SYNONYMS: N-Ethoxymethyl-N-(2-methyl 6 ethylphenyl)chloracetamide, acetochlor.

STUDY NUMBER: 87/SUC0012/0702.

SPONSOR: ICI Americas Inc., Wilmington, DE.

TESTING FACILITY: Life Science Research Ltd., Suffolk, England.

TITLE OF REPORT: SC-5676: 78 Week Feeding Study in CD-1 Mice.

AUTHOR(S): S.J. Amyes.

REPORT ISSUED: June 9, 1989.

CONCLUSION: In a 78-week feeding study designed to evaluate the carcinogenic potential of SC-5676, groups of 50 CD-1 mice/sex/dose were administered the test material at concentrations of 0, 10, 100, or 1000 ppm.In males, a dose-related increase in absolute and relative (to body weight) kidney weight was observed and was accompanied by significant increases in renal tubular basophilia at all dietary levels in males. In females, the only compound-related finding was a significant increase in anterior polar vacuoles in the lens of the eye at the high-dose level. Under the conditions of this study, the dietary exposure of SC-5676 resulted in a significant increase in pulmonary adenomas in female mice, and significant positive trends toward the development of pulmonary adenomas in both males and females. However, a definitive assessment of the carcinogenic potential was not possible because laboratory historical control data and a definitive characterization of pulmonary tumors, i.e., site and type, were not provided. Therefore, until these data are provided, the reviewers cannot make a definitive assessment of the carcinogenic potential of SC-5676.

Based on these results, the LOEL for systemic toxicity in males is 10 ppm (1.1 mg/kg/day); a NOEL was not established. In females, the NOEL and LOEL for systemic toxicity were 100 (13 mg/kg/day) and 1000 ppm (135 mg/kg/day), respectively.

The Maximum Tolerated Dose was not achieved in this study. Although increased kidney weight associated with tubular basophilia was observed in male mice at the 10ppm dose level, this effect was not considered sufficient for an MTD in this study. Review of a six-week range finding study in mice with acetochlor (Life Science Res. report # 85/SUC008/496) showed decreases in body weight gain of 9% and 12% at 600ppm and 1200ppm acetochlor, respectively, for male mice. In female mice from this study, a significant decrease in body weight gain (21%) was not observed until the 2400ppm dose level. Thus, based upon the results of the range-finding study, the MTD can be considered to have been achieved for male mice, but not for female mice.

CORE CLASSIFICATION: Supplementary; this study does not meet the minimum requirements set forth under guideline 83.2 for a carcinogenicity study in mice. This study may be upgraded upon submission and review of the additional data.

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A. MATERIALS:

1. Test compound: SC-5676; Description - Dark brown viscous liquid; Batch Nos - 1 and 3; Purity - 90.5%.

2. Test animals: Species - Mouse; Strain - CD-1; Age - 35-42 days at study initiation; Weight - Males, 23-31 and Females, 20-27 g at study initiation; Source - Charles River (UK) Ltd., Kent, England.

3. Mice were individually housed in suspended polypropylene cages with stainless steel mesh bottoms. Wood shavings were used as bedding. Temperature and relative humidity were maintained at approximately 21°C and 55% throughout the study. A minimum of 20 air changes/hour and a 12-hour light/12-hour dark cycle was achieved.

4. Animals received food (Laboratory Animal Diet No. 2; Labsure, Cambridgeshire, England) and water ad libitum.

5. Statistics: The following procedures were utilized in analyzing the numerical data:

-Body weight gain, hematology, and organ weight data--Student's t-test using a pooled within-treatment error variance;

-Mortality--Cox's test and Tarone's extension of Cox's test (analysis of trend). Adjusted mortality was estimated using the Kaplan-Meier method; and

-Ophthalmic and gross and microscopic pathological findings (nonneoplastic and neoplastic lesions)--Fisher's Exact Probability test.

6. Signed Quality Assurance and GLP Compliance statements, dated June 9, 1989, and a No Data Confidentiality Claim statement, dated June 25, 1990, were presented.

B. STUDY DESIGN:

1. Selection of dietary levels: Dietary concentrations were chosen based on the results of a preliminary rangefinding study in which mice (strain and number/sex/group not reported) were fed diets containing 300, 600, 1200, 2400, 4800, or 9600 ppm for 6 weeks. At 1200 ppm or higher, reductions in body weight gain (≥12%) and red cell characteristics were observed in males. Females receiving 2400 ppm had severe reductions (20%) in body weight, but females administered 1200 ppm were not affected. Males receiving 600 ppm exhibited reduced body weight gain and increased relative kidney weight. At 300 ppm, slight reductions (11%) in body weight were also observed.

2. Animal assignment: Animals were assigned using a computer-generated randomization procedure to the following test groups:

Test Group	Dietary Concentration (ppm)	Main Study 78 Weeks		Interim Sac. 52 Weeks	
		Males	Females	Males	Females
Control	0	50	50	10	10
Low (LDT)	10	50	50	10	10
Mid (MDT)	100	50	50	10	10
High (HDT)	1000	50	50	10	10

The test material was administered continuously in the diet for 78 weeks.

3. Diet preparation: Test diets were prepared weekly and stored at -20°C until use. Homogeneity of the test material in diets containing the lowest and highest concentrations was determined prior to study initiation. Stability of the test material in the low-dose diet after 7 and 14 days of storage at ambient temperature was determined prior to initiation of the study and again assayed after storage for 0 and 7 days (4 days at -20°C and 3 days at room temperature) during week 18 of the main study. Samples of test diets were analyzed for concentration during weeks 1, 13, 26, 39, 52, 65, and 78.

Results: Preliminary stability analysis indicated that the low dose (10 ppm) was unstable; 21-23% of the test material was lost after 14 days of storage at room temperature. Therefore, the test diets for the main study were stored at -20°C until use, and diet was replaced in the feeders every 4 days. This appeared to reduce the stability problem; no significant loss in active ingredient was detected after storage and feeding procedures were changed.

Homogeneity of the test diets was acceptable; aliquots were within 3 to 7% of each other, and the coefficient of variation ranged from 3.9 to 4.9%. Concentrations of the test diets were within acceptable ranges; actual concentrations ranged from -15 to +12% of target concentrations.

C. METHODS AND RESULTS:

1. Observations: Animals were inspected twice daily for clinical signs of toxicity and mortality. Furthermore, animals were subjected to detailed physical examinations weekly to detect palpable masses.

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Results: Mortality is summarized in Table 1. A slight increase (32%) in mortality was observed in high-dose males when compared with controls (20%); however, the increase was not statistically significant. Furthermore, a similar increase was not observed in females. The clinical signs observed with similar frequency in all test groups, including controls, during the study were those commonly seen in mice of this strain and age and therefore were not considered to be compound related. Palpable swellings noted during weekly clinical examinations occurred with similar frequency in control and test groups and were unrelated to treatment.

2. Body weight: Animals were weighed at study initiation, once weekly for the first 14 weeks, and bimonthly for the remainder of the study.

Results: Body weight gain data are summarized in Table 2. No statistically significant reductions in body weight or body weight gain were observed during the study. Slight increases in total body weight gain were observed in low-dose males and mid-dose females.

3. Food consumption and compound intake: Food consumption was determined weekly during the study. Efficiency was calculated at four weekly intervals for the first 12 weeks of the study; compound intake was calculated using food consumption and body weight data.

Results: Food consumption data are summarized in Table 3. No changes in food consumption or food efficiency were observed in the test groups relative to controls. The mean daily dosages, based on percent active ingredient, were approximately 0, 1.1, 11, and 116 mg/kg/day for males and 0, 1.4, 13, and 135 mg/kg/day for females from the control, low-, mid-, and high-dose groups, respectively.

4. Ophthalmological examination: Ophthalmic examinations were performed prior to study initiation on all animals using a Fisons binocular indirect ophthalmoscope and 0.5% tropicamide. After weeks 13, 24, 50, and 76, the eyes from all animals in the control and high-dose groups were similarly examined. Prior to study termination at week 79, ophthalmic examination of all surviving animals was performed.

Results: Ophthalmic findings after 76 weeks of treatment are summarized in Table 4. At 13 and 24 weeks, ophthalmic findings occurred with similar frequency in control and high-dose groups. At the 50-week interval, a statistically significant increase ($p < 0.05$) in the incidence of hyaloid remnant was observed in high-dose males (40/55) when compared with controls (28/56). This was not considered to be compound related, however, because incidences of hyaloid remnant observed in control and high-dose females were similar to that observed in high-dose males, suggesting that the low incidence seen in

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TABLE 1. Summary of Cumulative Mortality (Percent Survival) for Mice (Main Study) Fed SC-5676 for 78 Weeks[a]

Dietary Concentration (ppm)	Study Week: 18	26	52	76	80+[b]
			MALES		
0	0	0	3(94)	9(82)	10(80)
10	0	0	1(98)	11(78)	11(78)
100	0	0	3(94)	11(78)	14(72)
1000	0	2(96)	5(90)	16(68)	16(68)
			FEMALES		
0	0	0	2(96)	14(72)	17(66)
10	0	0	3(94)	7(86)	9(82)
100	0	0	3(94)	10(80)	12(76)
1000	0	0	1(98)	13(74)	13(74)

[a]Data were extracted from study No. 87/0702, Table 2.

[b]These animals were awaiting terminal sacrifice.

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TABLE 2. Summary of Body Weight Gain Data (g) in Mice Fed SC-5675 for 78 Weeks[a]

Dietary Concentration (ppm)	Study Week: 0-13	13-52	52-78	0-78
		MALES		
0	12.7	7.9	1.4	20.8
10	13.4	8.4	0.8	24.1
100	12.9	6.2	0.6	19.4
1000	11.9	7.9	0.3	20.2
		FEMALES		
0	7.3	4.8	2.6	15.2
10	7.6	4.3	2.1	12.7
100	8.2	4.8	3.2	16.3
1000	8.2	3.6	2.2	14.2

[b]Body weight gains were calculated by the reviewers using individual animal data, Appendix 5.

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TABLE 3. Summary of Food Consumption Data (g/mouse/week) in Mice Fed SC-5676 for 78 Weeks

Dietary Concentration (ppm)	Study Week: 1	7	14	28	50	64	78
			MALES				
0	39	39	35	35	35	34	34
10	39	38	38	36	36	35	36
100	38	38	38	34	35	35	34
1000	39	38	37	35	36	34	35
			FEMALES				
0	35	38	35	35	35	32	32
10	35	37	35	33	33	34	34
100	34	37	36	32	32	31	31
1000	35	38	35	34	34	30	30

[a]Data were extracted from study No. 87/0702, Table 4.

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TABLE 4. Summary of Ocular Effects Observed at 76 Weeks in Surviving Mice Fed SC-5676 Continuously for 78 Weeks[a]

	Dietary Concentration (ppm)							
	Males				Females			
Finding	0	10b	100[b]	1000	0	10[b]	100[b]	1000
Cornea:								
Superficial opacity	9(22)[c]	7(18)	11(30)	10(29)	13(36)	15(36)	5(13)*	10(27)
Lens:								
Hyaloid remnant	14(34)	7(18)	6(16)	15(44)	10(28)	6(14)	5(13)*	14(38)
Anterior polar vacuole(s)	10(24)	11(28)	12(32)	9(29)	7(19)	10(24)	12(32)	20(54)**
Anterior polar opacity	2(5)	4(10)	1(3)	1(3)	5(14)	4(10)	0(0)	1(3)
Posterior polar vacuole(s)	2(5)	2(5)	2(5)	0(0)	0(0)	3(7)	5(13)	1(3)
Posterior polar opacity	2(5)	3(8)	2(5)	3(9)	13(36)	4(10)**	13(34)	17(46)

[a]Data were extracted from study No. 87/0702, Table 7D.
[b]Examination of the 10- and 100-ppm groups was performed during week 78.
[c]Number in parentheses represents the % incidence.

* Significantly different from controls (0.05).
** Significantly different from controls (0.01).

control males at this interval was atypical. Furthermore, the increase did not persist to the end of the study. Also observed at this interval was a significant increase ($p < 0.01$) in the incidence of rosettes in high-dose females. Since a similar increase was not observed at study termination, this was not considered to be compound related. No other adverse effects were observed at 50 weeks.

At the 76-week interval, a significant increase (<0.01) in the incidence of vacuoles in the anterior polar region of the lens was observed in high-dose females. According to the study author, ophthalmic examination of females from the low- and mid-dose groups did not reveal a similar increase; however, although the incidences were not statistically significant, a dose-related pattern was evident. No increase in the incidence of vacuoles in the anterior polar region of the lens was observed in males. In addition, the incidence of anterior polar opacity was not inereased.

Hematology analysis: Blood was collected from the retro-orbital sinus during week 51 from all animals selected for interim sacrifice and during weeks 78 or 79 from 20 animals/sex/group for hematology analysis. The animals selected were nonfasted and lightly anaesthetized with ether. The CHECKED (X) parameters were examined.

a. Hematology:

X Hematocrit (HCT)*
X Hemoglobin (HGB)*
X Erythrocyte count*
X Leukocyte count*
X Platelet count*
X Leukocyte differential count*
X Packed cell volume (PCV)

Coagulation: Thromboplastin time (PT)*
X Reticulocyte count (RETIC)
Red cell morphology
X Mean corpuscular HGB concentration (MCHC)
X Mean corpuscular volume (MCV)
X Mean corpuscular hemoglobin (MCH)

* Required for subchronic and chronic studies

Results: Hematology data from terminal sacrifice are summarized in Table 5. At the 51-week interval, packed cell volume, hemoglobin, and erythrocyte count were slightly reduced (7%) in males and significantly reduced ($p < 0.05$ or 0.01) in females from the high-dose group. After 77 weeks, packed cell volume and erythrocyte count were significantly reduced ($p < 0.05$) in mid- and high-dose males. In females, statistically significant reductions ($p < 0.05$) in neutrophil count at the low-dose and MCHC and MCV at the mid-dose were observed.

6. Sacrifice and Pathology: All animals that died or were sacrificed moribund or on schedule were subjected to a gross pathological examination. The CHECKED (X) tissues were collected for histological examination and fixed in 4% neutral buffered formaldehyde solution, except for the eyes with optic nerve attached and Harderian gland, which were saved in Davidson's fixative. In addition, the (XX) organs were weighed.

TABLE 5. Summary of Hematology Data Obtained During Terminal Sacrifice from Mice Fed SC-5676 in the Diet for 78 Weeks[a]

Dietary Concentration (ppm)	PCV (%)	Hb (g%)	RBC (mil/cmm)	MCHC (%)	MCV (cμ)	MCH (pg)	Platelets (1000/cmm)
			MALES[b]				
0	42 ± 6	14.7 ± 2.4	8.5 ± 1.0	35 ± 1	50 ± 3	17 ± 1	607 ± 106
10	40 ± 5	14.0 ± 1.7	8.1 ± 1.1	35 ± 0	50 ± 2	18 ± 1	700 ± 159
100	39 ± 4*	13.7 ± 1.4	7.8 ± 1.0*	35 ± 1	50 ± 3	18 ± 1	651 ± 163
1000	39 ± 4*	13.6 ± 1.5	7.7 ± 1.1*	35 ± 1	51 ± 3	18 ± 1	722 ± 163*
			FEMALES[b]				
0	40 ± 6	13.9 ± 2.3	7.9 ± 1.4	35 ± 1	51 ± 2	18 ± 1	524 ± 158
10	42 ± 5	14.6 ± 1.5	8.3 ± 1.0	35 ± 1	50 ± 2	17 ± 1	472 ± 88
100	40 ± 3	14.3 ± 1.2	8.3 ± 0.6	35 ± 1*	49 ± 3*	17 ± 1	465 ± 127
1000	41 ± 4	14.2 ± 1.4	8.1 ± 0.8	35 ± 1	50 ± 2	18 ± 1	509 ± 114

[a]Data were extracted from study No. 87/0702, Table 8B.
[b]Blood was collected from males during week 77 and from females during week 78.

*Significantly different from controls ($p < 0.05$).

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Digestive System	Cardiovasc./Hemat.	Neurologic
X Tongue	X Aorta*	XX Brain*)
X Salivary glands*	X Heart*	X Periph. nerve*
X Esophagus*	X Bone marrow*	X Spinal cord*
X Stomach*	X Lymph nodes*	X Pituitary*
X Rectum*	X Spleen*	X Eyes* (optic nerve)
X Colon*	X Thymus	
X Cecum*		
X Ileum*		
X Jejunum*		
X Duodenum*		
XX Liver*)		
X Gallbladder*		
X Pancreas*		

Respiratory	Urogenital	Glandular
X Trachea*	XX Kidneys*)	XX Adrenals*
X Lung*	X Urinary bladder*	Lacrimal gland
X Nasal cavity	XX Testes*)	X Mammary gland*
	X Epididymis*	X Thyroid gland*
	X Prostate*	X Parathyroid*
	X Seminal vesicle*	X Harderian gland
	X Ovaries*	
	X Uterus*	
	Vagina	

Other
X Bone (sternum & femur)*
X Skeletal muscle*
X Skin*
X All gross lesions & masses*

* Recommended by Subdivision F (October 1982) Guidelines.
\+ Organ weight required in chronic studies.

The above tissues, except for the tongue, bone marrow, and mammary gland, from all control and high-dose animals dying or sacrificed moribund or on schedule and any animals from the low- or mid-dose groups dying or sacrificed moribund during the study were microscopically examined, as were gross lesions, kidney, liver, and lung from low- and mid-dose animals sacrificed on schedule.

a. Organ weight: Organ weight data collected following terminal sacrifice are summarized in Table 6.

At the interim sacrifice, a compound-related and statistically significant increase ($p < 0.01$) in relative (to body weight) kidney weight, associated with nephropathy in 4/9 animals examined, was observed in high-dose males. The observed significant increases ($p < 0.05$) in relative brain and adrenal weight in high-dose males may have been due to the reduction (12%) in body weight since no microscopic changes were observed; therefore, these reductions were not considered to be compound related. No other significant changes in organ weight were observed.

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TABLE 6. Summary of Absolute and Relative Organ Weights in Mice Fed SC-5676 Continuously for 78 Weeks[a]

	Dietary Concentration (ppm)							
	Males				Females			
Organ	0	10	100	1000	0	10	100	1000
Terminal Body Weight (g)	47.0	48.3	46.1	45.3	37.4	36.4	38.1	36.7
Kidney:								
Absolute (g)	0.85	0.92*	0.96**	1.12***	0.53	0.56	0.55	0.49*
Relative (%)	1.83	1.93	2.12*	2.50***	1.42	1.56	1.46	1.36
Liver:								
Absolute (g)	2.4	2.9*	2.6	2.8	1.8	1.8	1.8	1.9
Relative (%)	5.07	5.96*	5.72	6.27*	4.90	5.01	4.77	5.18
Adrenals:								
Absolute (mg)	3.0	3.0	3.0	3.0	7.0	7.0	7.0	7.0
Relative (%)	5.7	6.0	5.9	6.5	18.2	18.7	18.6	18.8
Brain:								
Absolute (g)	0.52	0.51	0.51	0.51	0.52	0.53	0.52	0.50*
Relative (%)	1.12	1.08	1.12	1.14	1.45	1.50	1.41	1.39

[a]Data were extracted from study No. 87/0702, Table 12.

*Significantly different from controls ($p < 0.05$).
**Significantly different from controls ($p < 0.01$).
***Significantly different from controls ($p < 0.001$).

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At terminal sacrifice, dose-related and statistically significant increases in absolute kidney weight were observed in low-, mid-, and high-dose males when compared with controls. Relative kidney weight was also significantly increased ($p < 0.001$) in males at the mid- and high-dose levels. In addition, dose-related increases in absolute and relative liver weight were observed in males. The increases in liver weight were accompanied by histopathological findings which probably affected the organ weight in low-dose animals. However, after exclusion of high-dose animals with hepatic carcinomas, adenomas, or hyperplastic nodules, liver weight was still significantly higher than controls. Other significant changes in organ weight were not considered to be compound related.

b. Gross pathology: Statistically significant increases in the incidences of enlarged kidneys (verified by increase in kidney weight) in high-dose males ($p < 0.05$) and distension of the coagulating gland of the seminal vesicles in low-dose males ($p < 0.01$) were observed. In addition, a slight increase in dark Harderian glands was observed in treated females when compared with controls (9, 28, 21, and 19 for control, low-, mid-, and high-dose groups, respectively). However, the reviewers considered only the enlarged kidneys to be compound related; the other findings were not corroborated by histopathological evidence and are commonly seen in mice of this age and strain.

c. Microscopic pathology: Nonneoplastic and neoplastic lesions found in the lungs, liver, and kidneys are summarized in Tables 7 and 8, respectively.

1. Nonneoplastic - At the 52-week interim sacrifice, nephropathy was observed in 44% (4/9) of high-dose males, compared with 0% of controls. Twenty percent of the high-dose females were affected, compared with 10% of control females.

Statistically significant increases in the incidences of interstitial fibrosis, hyaline cysts, and cortical mineralization were observed in high-dose males when compared with controls. In addition, dose-related and statistically significant increases in the incidence of tubular basophilia were observed in all treatment groups compared to controls. Similar changes were not noted in females. Other significant changes in incidences of nonneoplastic findings in the adrenals, salivary glands, lungs, ovaries, and stomach were not considered by the study author to be compound related. However, a statistically significant increase in bronchiolar hyperplasia was observed in mid- and high-dose males, which may be associated with the increased incidence of pulmonary tumors.

However, although a statistically significant increase in pulmonary adenomas was noted in high-dose females, the incidence of bronchiolar hyperplasia was similar between control and high-dose females, while being slightly higher in low- and mid-dose females.

2. Neoplastic - At the interim sacrifice, a pulmonary adenoma was observed in one high-dose female and one mid-dose male. In addition, a hepatocytic adenoma was observed in 1/10 low-dose males. The number of animals (incidence) dying or killed during the study with pulmonary adenomas is presented below; all the animals developing adenomas survived to at least week 63.

Dose	0	10	100	1000
Males	0	0	1(29)	3(19)
Females	0	1(10)	0	1(7)

In animals assigned to terminal sacrifice (included animals found dead or sacrificed prior to study termination), a significant increase ($p < 0.05$) in the incidence of pulmonary adenomas was observed in high-dose females when compared with controls. Moreover, although not statistically significant, an increased incidence was also observed in mid- and high-dose males and mid-dose females. As a result, a significant positive trend was observed in both male and female mice. Combining pulmonary carcinomas and adenomas did not significantly change the pattern; although the incidence in high-dose females was no longer statistically significant, statistically significant positive trends ($p < 0.05$) were observed in both males and females. Hemangiosarcomas of the liver were observed in 2/50 high-dose males; although historical control incidences were not presented with the study report, the incidence of hemangiosarcomas is slightly above the range normally seen in mice of this age and strain (0-2.8%). Slight increases in the incidences of other neoplasms, including hepatocytic adenomas or carcinomas and malignant lymphoma in the hematopoietic tissue, were observed in treated males when compared with controls, but the incidences were within the range generally observed in animals of this strain and age and therefore, were not considered to be compound related.

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TABLE 7. Summary of Nonneoplastic Lesions in the Lungs, Kidney and Liver of Male Mice Fed SC-5676 Continuously for 78 Weeks[a]

	Dietary Concentration (ppm)			
Finding	0	10	100	1000
No. examined	50	50	50	50
Lung:				
Bronchiolar hyperplasia	5(13)[b]	4(10)	14(39)*	13(38)*
Kidney:				
Cortical mineralization	12(30)	12(31)	11(31)	23(68)**
Hyaline cast(s)	5(13)	4(10)	6(17)	12(35)*
Tubular basophilia	2(5)	13(33)*	10(28)**	15(44)**
Interstitial fibrosis	6(15)	7(18)	10(28)	17(50)*
Tubular epithelial hyper.	0	0	1(3)	4(12)*
Liver:				
Nodular hyperplasia	3(8)	6(15)	2(6)	2(6)
Focal hepatocytic hyper.	0	2(5)	0	1(3)
Periacinar hyperplasia	8(20)	11(28)	6(17)	9(26)

[a]Data were extracted from study No. 87/0702, Table 17.
[b]Numbers in parentheses represent % incidence.

* Significantly different from controls ($p < 0.05$).
** Significantly different from controls ($p < 0.01$).

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TABLE 8. Summary of Neoplastic Lesions in Mice Fed SC-5676 Continuously for 78 Weeks[a]

Finding	Dietary Concentration (ppm) 0	10	100	1000
	MALES			
No. examined	50	50	50	50
Kidney:				
Adenoma	0	2(4)[b]	1(2)	1(2)
Liver:				
Hepatocytic adenoma	2(4)	4(8)	3(6)	5(10)
Hepatocytic carcinoma	1(2)	3(6)	2(4)	3(6)
Adenoma + carcinoma[c]	3(6)	7(14)	5(10)	8(16)
Hemangiosarcoma	0	0	0	2(4)
Lungs:				
Pulmonary carcinoma	5(10)	4(8)	3(6)	4(8)
Pulmonary adenoma	5(10)*	4(8)	11(22)	12(24)
Adenoma + carcinoma[c]	10(20)*	7(14)	14(28)	16(32)
	FEMALES			
No. examined	50	50	50	50
Kidney:				
Adenoma	0	0	0	0
Liver:				
Hepatocytic adenoma	1(2)	2(4)	0	1(2)
Hepatocytic carcinoma	0	1(2)	0	0
Adenoma + carcinoma[c]	1(2)	3(6)	0	1(2)
Hemangiosarcoma	0	0	1(2)	0
Lungs:				
Pulmonary carcinoma	4(8)	0	2(4)	4(8)
Pulmonary adenoma	1(2)*	3(6)	5(10)	7(14)*
Adenoma + carcinoma[c]	5(10)*	3(6)	7(14)	11(22)

[a]Data were extracted from study No. 87/0702, Table 24. Includes only mice scheduled for sacrifice at 78 weeks.
[b]Numbers in parentheses represent % incidence.
[c]Calculated by the reviewers and analyzed using Fisher's Exact test and Cochran-Armitage trend test.

* Significantly different from controls ($p < 0.05$). Significant trends are denoted at the controls.

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D. REVIEWERS' DISCUSSION/CONCLUSIONS:

The data reveal a clear sex-related difference in systemic toxicity. In males, ingestion of SC-5676 resulted in dose-related increases in kidney effects which were manifested as increases in absolute and relative kidney weights and were associated with increases in the incidence of renal tubular basophilia at all dietary levels. In females, the only compound-related systemic effect was an increase in the incidence of anterior polar vacuoles in the lens of the eye at the high-dose level. Based on the dose-related increases in kidney weight and incidence of tubular basophilia, the LOEL for systemic effects in male mice was 10 ppm (1.1 mg/kg/day); the NOEL was not established. For female mice, the NOEL and LOEL for systemic toxicity were 100 (13 mg/kg/day) and 1000 ppm (135 mg/kg/day), respectively, based on an increase in ocular effects at 1000 ppm.

The Maximum Tolerated Dose was not achieved in this study. Although increased kidney weight associated with tubular basophilia was observed in male mice at the 10ppm dose level, this effect was not considered sufficient for an MTD in this study. Review of a six-week range finding study in mice with acetochlor (Life Science Res. report # 85/SUC008/496) showed decreases in body weight gain of 9% and 12% at 600ppm and 1200ppm acetochlor, respectively, for male mice. In female mice from this study, a significant decrease in body weight gain (21%) was not observed until the 2400ppm dose level. Thus, based upon the results of the range-finding study, the MTD can be considered to have been achieved for male mice, but not for female mice.

A significant increase in the incidence of pulmonary adenomas was observed in females. This was associated with significant positive trends in both males and females toward the development of pulmonary adenomas. However, a significant increase in the incidence of pulmonary carcinomas was not observed, and the incidence of combined pulmonary adenomas and carcinomas was not statistically significant in high-dose females, although statistically significant positive trends were still evident for both males and females. Since the study was terminated at 78 weeks (19.5 months), even though survival was greater than 68% in all groups, the observation period may have been insufficient for development of carcinomas. Conversely, the tumor incidences observed in the lungs may have been within historical control ranges. However, historical control data for the laboratory were not presented. Furthermore, the tumors were described as pulmonary adenomas or carcinomas without further characterizing them as to location in the lung; consequently, published historical control data for this strain of mouse were of little use in evaluating spontaneous tumor incidences. Therefore, until historical control data and definitive characterization of the pulmonary tumors, i.e., type and site, are provided, the reviewers are unable to make an assessment of the carcinogenic potential of SC-5676; the study is classified as supplementary and may be upgraded upon submission and review of the required data.

E. STUDY DEFICIENCIES:

The following deficiencies in the conduct or reporting of the study were noted:

1. Historical control data on histopathological findings were not presented.

2. Definitive characterization, i.e., type and site, of pulmonary tumors was not performed.

F. CLASSIFICATION: CORE Supplementary data.
Systemic NOEL (Males) = Not established.
Systemic LOEL (Males) = 10 ppm (approx. 1.1 mg/kg/day).
Systemic NOEL (Females) = 100 ppm (approx. 13 mg/kg/day).
Systemic LOEL (Females) = 1000 ppm (approx. 135 mg/kg/day).

Maximum Tolerated Dose- achieved in male mice, not achieved in female mice.

TABLE 28

Historical control data for selected tumours of the kidneys, liver, lungs and haemopoietic tissue in CD-1 mice generated at LSR

Code	:	017A	017B	022
Commenced (year)	:	85	85	86
Source	:	--- Charles River UK ---		
Housing (per cage)	:	1	1	4
Study duration (weeks)	:	78	78	78
No. of mice examined	:	50	50	60
		MALES		
Tissue and neoplasm				
Kidney				
Adenoma		0	0	0
Liver				
Haemangioma		2	1	0
Haemangiosarcoma		0	0	0
Hepatocytic adenoma		9	6	1
Hepatocytic carcinoma		2	2	5
Lungs				
Pulmonary adenoma		5	2	7
Pulmonary carcinoma		5	6	2
Haemopoietic tissue				
Malignant lymphoma		4	2	3
		FEMALES		
Tissue and neoplasm				
Lungs				
Pulmonary adenoma		2	2	2
Pulmonary carcinoma		2	4	1