

Histopathology	Males					Females				
	0	24	48	96	192	0	24	48	96	192
Ovaries						10	0	2	10	10
Vacuolation, sex cord										
Mild						0	0	0	0	5
Moderate						0	0	0	0	5
Vacuolation, corp lutea										
Minimal						0	0	0	0	1
Mild						0	0	0	0	2
Moderate						0	0	0	0	6
Necrosis, granulosa cell										
Minimal						0	0	0	0	4
Mild						0	0	0	0	3
Moderate						0	0	0	0	2
Pancreas	10	0	0	10	10	10	0	0	10	10
Vacuolation, epithelium exocrine										
Minimal	0			0	2	0			0	2
Mild	0			0	8	0			0	8
Parathyroid glands	10	0	7	7	10	10	0	9	10	10
Vacuolation, chief cell										
Minimal	0		0	0	2	0		0	0	0
Pituitary gland	10	0	10	9	10	10	0	9	10	10
Vacuolation, pars anterior										
Minimal	0		0	6	7	0		0	7	4
Mild	0		0	0	3	0		0	0	5
Moderate	0		0	0	0	0		0	0	1
Salivary gland	10	0	0	10	10	10	0	0	10	10
Vacuolation, ductular										
Minimal	0			0	5	0			0	5
Mild	0			0	1	0			0	1
Vacuolation, acinar										
Minimal	0			0	0	0			0	0
Atrophy, sublingual										
Mild	0			0	0	0			0	0
Cellular infiltration, mononuclear cell										
Minimal	0			0	0	0			0	0
Seminal vesicles	10	1	0	10	10					
Vacuolation, epithelium										
Mild	0	0		0	10					
Skeletal muscle	10	0	0	10	10	10	0	0	10	10
Vacuolation, myofiber										
Minimal	0			0	7	0			0	2
Mild	0			0	3	0			0	6
Moderate	0			0	0	0			0	2
Necrosis, myofiber										
Minimal	0			0	1	0			0	2
Skin	10	10	10	10	10	10	10	10	10	10
Vacuolation, epithelium										
Minimal	0	0	0	4	2	0	0	0	4	1
Mild	0	0	0	0	5	0	0	0	0	6

Histopathology	Males					Females				
	0	24	48	96	192	0	24	48	96	192
Dose group (mg/kg)	0	24	48	96	192	0	24	48	96	192
Moderate	0	0	0	0	0	0	0	0	0	3
Panniculitis, granulomatous mild	0	0	0	0	1	0	0	0	0	0
Harderian glands	10	10	10	10	10	10	10	10	10	10
Pigment accumulation										
Minimal	0	0	0	3	0	0	0	3	0	0
Mild	0	0	2	5	5	0	0	2	9	5
Moderate	0	0	0	0	2	0	0	0	0	5
Cellular infiltration, macrophage										
Minimal	0	0	0	0	0	0	0	0	0	1
Stomach	10	0	0	10	10	10	0	10	10	10
Vacuolation, epithelium										
Minimal	0			0	4	0		0	3	3
Mild	0			0	3	0		0	0	4
Cellular infiltration, granulomatous										
Minimal	0			0	0	0		0	0	1
Single cell necrosis, epithelium										
Minimal	0			0	1	0		0	0	1
Small intestine	10	0	10	10	10	10	0	10	10	10
Vacuolation, lymphoid nodule, macrophage										
Minimal	0		0	0	0	0		0	0	1
Vacuolation, lamina propria, macrophage										
Minimal	0		0	2	6	0		0	0	4
Mild	0		0	0	3	0		0	0	5
Vacuolation, epithelium										
Minimal	0		0	3	6	0		0	6	9
Spleen	10	0	10	10	10	10	0	10	10	10
Vacuolation, m-phage										
Minimal	0		0	0	5	0		0	0	8
Mild	0		0	0	3	0		0	0	1
Necrosis, lymphoid										
Minimal	0		0	0	2	0		0	0	5
Mild	0		0	0	0	0		0	0	2
Depletion, lymphoid										
Minimal	0		0	3	4	0		0	0	6
Mild	0		0	0	4	0		0	0	2
Moderate	0		0	0	2	0		0	0	0
Testes	10	0	0	10	7					
Cellular debris, spermatid										
Minimal	2			0	4					
Thyroid	10	0	10	10	10	10	0	10	10	10
Vacuolation										
Minimal	0		0	1	3	0		0	0	5
Mild	0		0	0	1	0		0	0	4

Histopathology	Males					Females				
	0	24	48	96	192	0	24	48	96	192
Moderate	0		0	0	2	0		0	0	0
Thymus	10	0	10	9	10	10	0	0	10	10
Vacuolation, m-phage										
Minimal	0		0	0	4	0			0	3
Mild	0		0	0	2	0			0	2
Necrosis, lymphoid										
Minimal	0		0	1	2	0			0	3
Mild	0		0	0	4	0			0	2
Moderate	0		0	0	0	0			0	1
Depletion, lymphoid										
Minimal	0		0	0	2	0			0	2
Mild	0		0	0	1	0			0	0
Moderate	0		0	0	2	0			1	1
Tongue	10	0	0	10	10	10	0	0	10	10
Vacuolation, myofiber										
Minimal	0			0	3	0			0	4
Mild	0			0	7	0			0	5
Moderate	0			0	0	0			0	1
Trachea	10	0	10	10	10	10	0	10	10	10
Vacuolation, epithelium										
Minimal	0		0	9	1	0			7	0
Mild	0		0	0	7	0			0	7
Moderate	0		0	0	2	0			0	3
Uterus						10	10	10	10	10
Vacuolation, epithelium, endometrium										
Minimal						0	0	0	0	9
Mild						0	0	0	0	1
Vacuolation, endometrium, m-phage										
Minimal						0	0	0	0	4
Mild						0	0	0	0	4
Moderate						0	0	0	0	1
Atrophy										
Minimal						0	0	0	0	4
Mild						0	0	0	0	1
Urinary bladder	10	0	10	10	10	10	0	0	9	10
Vacuolation, epithelium										
Minimal	0		0	6	1	0			0	4
Mild	0		0	0	9	0			0	6
Vagina						10	0	0	10	10
Vacuolation, epithelium, cervix										
Mild						0			0	10
Ectasia, gland, clitoris mild						0			0	1
Mammary glands						10	0	0	10	10
Vacuolation										
Minimal						0			0	1
Mild						0			0	2
Moderate						0			0	1

This study was performed in order to determine doses in a 2 year Phase 4 mouse carcinogenicity study. An MTD of 48 mg/kg was selected in males due to systemic phospholipidosis at this dose and a significant reduction of body weight gain as well as kidney necrosis associated with systemic phospholipidosis at the next highest dose of 96 mg/kg. The MTD for females appears to be 96 mg/kg due to systemic phospholipidosis at this dose and findings of necrosis associated with systemic phospholipidosis and a significant reduction in body weight gain at the next highest dose of 192 mg/kg.

## GENETIC TOXICOLOGY:

### Bacterial Mutagenicity Study of SCH 45581

Report No.: P-6609 Study No.: 99298 Volume: 44.11

*Study endpoint:* Mutagenicity  
*Study Dates:* Starting date 2/17/2000; report issued 5/23/2000  
*Testing Lab:* Schering-Plough Research Institute, Lafayette, NJ  
*Test Article:* SCH 45581 (Batch 76214-141-4) diluted in DMSO  
*GLP:* The study was accompanied by a signed GLP statement.  
*QA report:* Yes.

**Methods:** SCH 45581 (3-hydroxy-desloratadine), a metabolite of SCH 34117, was assayed in 5 Salmonella tester strains and 1 E. coli strains  $\pm$  metabolic activation by Aroclor 1254-induced rat liver S9 fraction. The following strains and positive controls were used in 2 plate incorporation tests:

Strain	Positive Controls Without S9 ( $\mu\text{g}/\text{plate}$ )	Positive Controls With S9 ( $\mu\text{g}/\text{plate}$ )
TA 1535	sodium azide (5)	2-aminoanthracene (2.5)
TA 97a	9-aminoacridine (75)	2-aminoanthracene (2.5)
TA 98	2-Nitrofluorene (5)	2-aminoanthracene (2.5)
TA 100	sodium azide (5)	2-aminoanthracene (2.5)
TA 102	Cumene hydroperoxide (200)	2-aminoanthracene (5)
WP2 uvrA	N-Ethyl-N'-nitro-N-nitrosoguanidine (2)	2-aminoanthracene (20)

SCH 45581 and positive controls were dissolved in DMSO. Doses for Trial 1 were selected based upon results of a previous bacterial mutagenicity study with SCH 34117 and the two mutagenicity assays were conducted at the following concentrations:

Bacterial strain	Phase	Trial 1 Doses (µg/plate)	Trial 2 Doses (µg/plate)	Trial 3 Doses (µg/plate)
TA 1535	nonactivation	94, 188, 375, 750, 1500	63,125,250, 500, 1000	16, 31, 63,125,250, 500
TA 97A	nonactivation	12, 23, 47, 94, 188	4, 8, 16, 31, 63	4, 8, 16, 31, 63, 125
TA 98	nonactivation	47, 94, 188, 375, 750	31, 63, 125, 250, 500	
TA 100	nonactivation	23, 47, 94, 188, 375	16, 31, 63, 125, 250	
TA 102	nonactivation	23, 47, 94, 188, 375	16, 31, 63, 125, 250	4, 8, 16, 31, 63, 125
WP2uvrA	nonactivation	94, 188, 375, 750, 1500	125, 250, 500, 1000, 200	
TA 1535	activation	94, 188, 375, 750, 1500	63,125,250, 500, 1000	
TA 97A	activation	12, 23, 47, 94, 188	8, 16, 31, 63, 125	
TA 98	activation	47, 94, 188, 375, 750	31, 63, 125, 250, 500	
TA 100, TA 10	activation	23, 47, 94, 188, 375	31, 63, 125, 250, 500	
WP2uvrA	activation	94, 188, 375, 750, 1500	125, 250, 500, 1000, 200	

The experiments were performed using triplicate plates at each concentration incubated for 48 hours ± S9. Cytotoxicity was evaluated based on a reduction in revertant colony counts by ~30%, inhibition of background bacterial lawn growth and "additional factors based on scientific judgment". Tests were valid if overnight bacterial cultures reached a density of at least  $5 \times 10^8$  cells/ml for *Salmonella typhimurium* strain, and approximately  $15 \times 10^8$  cells/ml for *E. coli*, the mean number of spontaneous revertant colonies/plate was within the range of the historical solvent control values of the same strain, the mean number of induced revertants/plate in the positive controls was at least three-fold greater than the mean of its concurrent solvent control for TA 1535 and at least two-fold greater than the mean of their respective concurrent controls for *E. coli* and other *Salmonella* strains, and at least three doses with revertants are required for data evaluation for each trial. Tests were positive that produced increases in revertant counts, as compared to solvent controls, with or without metabolic activation, in at least one of the six tester strains. The magnitude of increase was at least two-fold above the solvent control for strains TA 97A, TA 98, TA 100, TA 102 and WP2uvrA, and three-fold above the solvent control for strain TA 1535. In addition, a dose-response increase of revertant counts in treated plates above that of the solvent control was observed in at least two dose levels, and the increases were reproducible in independent trials.

**Results:** In the first mutagenicity trial, SCH 45581 did not increase revertant colony counts, ± S9 activation. Positive controls significantly increased the number of revertant colonies. In the nonactivation phase, cytotoxicity to revertant colonies was observed at 23 µg/plate and above for TA 97a, 94 and 375 µg/plate for TA 102, and at 750 µg/plate and above for TA 1535. Microcolonies were observed at 188 µg/plate for TA 102, at 375 µg/plate for TA 1535 and TA 100, at 188, 375 and 750 µg/plate for TA 98, and at 1500 µg/plate for WP2uvrA. Cytotoxicity to background lawn was observed at 375 µg/plate and above for TA 1535, at 188 µg/plate for TA97a and TA 98, at 188 µg/plate and above for TA 100, at 94 µg/plate and above for TA 102 and at 1500 µg/plate for WP2uvrA. In the activation phase, cytotoxicity to revertant colonies was observed at 23 µg/plate and above for TA 97a, 188 µg/plate and above for TA 102, 375 µg/plate for TA 100, 750 µg/plate and above for TA 1535, and at 1500 µg/plate and above for WP2uvrA. Microcolonies were observed at 750 µg/plate for TA 98 and cytotoxicity to background lawn was observed at 375 µg/plate for both TA 100 and TA 102, at 750 µg/plate and above for TA 1535, and at 750 µg/plate for TA 98.

SCH 45581 did not increase revertant colony counts,  $\pm$  S9 activation, in the second trial. However, the revertant counts in strain TA 97a were below historical control levels and were repeated in Trial 3. In the nonactivation phase, cytotoxicity to revertant colonies was observed at 16  $\mu$ g/plate and above for TA 97a, 63  $\mu$ g/plate for TA 100, 125  $\mu$ g/plate for TA 98, and at 500  $\mu$ g/plate and above for TA 1535 and WP2uvrA. Microcolonies were observed at 63 and 125  $\mu$ g/plate for TA 102, at 125 and 250  $\mu$ g/plate for TA 1535, at 250  $\mu$ g/plate and above for TA 98, and at 125  $\mu$ g/plate and above for TA 100. Cytotoxicity to background lawn was observed at 16  $\mu$ g/plate and above for TA 98, at 63  $\mu$ g/plate and above for TA 1535, at 125  $\mu$ g/plate and above for TA 100, at 250  $\mu$ g/plate and above for TA 98 and at 2000  $\mu$ g/plate for WP2uvrA. Strains TA 1535 and 102 were repeated in Trail 3 due to cytotoxicity at all doses tested. In the activation phase, cytotoxicity to revertant colonies was observed at 31  $\mu$ g/plate and above for TA 97a, 250  $\mu$ g/plate and above for TA 100 and 102, 500  $\mu$ g/plate for TA 98, and at 1000  $\mu$ g/plate and above for WP2uvrA. Microcolonies were observed at 500  $\mu$ g/plate for TA 98 and at 1000  $\mu$ g/plate for TA 1535. Cytotoxicity to background lawn was observed at 500  $\mu$ g/plate for both TA 100 and TA 98, at 1000  $\mu$ g/plate for TA 1535, and at 2000  $\mu$ g/plate for WP2uvrA.

In the third trial, SCH 45581 did not increase revertant colony counts without activation in strains TA 97a, TA 102 and TA 1535. Cytotoxicity to revertant colonies was observed at 31  $\mu$ g/plate and above for TA 97a, and at 125  $\mu$ g/plate for TA 102. Microcolonies were observed at 500  $\mu$ g/plate for TA 1535. Cytotoxicity to background lawn was observed at 125  $\mu$ g/plate for both TA 97a and 102, and at 250  $\mu$ g/plate and above for TA 1535.

Thus, SCH 45581, up to 1000  $\mu$ g/plate in *Salmonella* strains and up to 2000  $\mu$ g/plate in *E. coli*, was negative in the bacterial mutation test (Ames assay) using plate incorporation, in concurrence with the sponsor's conclusion.

#### Mouse bone marrow erythrocyte micronucleus study of SCH 45581

Schering Study No.: 99539      Volume: 44.11

**Study endpoint:** Clastogenicity  
**Study Dates:** Starting date 12/13/1999; report issued 5/22/2000  
**Testing Lab:** Schering Plough Research Institute, Lafayette, NJ  
**Test Article:** SCH 45581 (Batch No. 75669-17) in 0.4% methylcellulose  
**GLP:** The study was accompanied by a signed GLP compliance statement.  
**QA report:** Yes.

**Methods:** SCH 45581 was evaluated for its potential to induce micronuclei in the bone marrow of male and female Crl:CD-1 IBR VAF/Plus mice (6 weeks old; 19.6-31.9 g; 6/sex/dose/sacrifice time) following two consecutive daily IP doses of 10, 20 or 40 mg/kg (dose volume: 10 ml/kg; concentrations: mg/ml). Dose selection was based upon dose-ranging studies. In the first study excessive mortality was observed following a single IP doses of 125-2000 mg/kg (10 ml/kg). In the second study, mice were administered two consecutive daily IP doses of 6.25, 12.5, 25, 50 and 100 mg/kg. Mortality was observed at doses of 50 and 100 mg/kg in males and at the high dose in females. The PCE/NCE ratio was reduced by 19 and 61% at doses

of 25 and 50 mg/kg, respectively, in males and 18 and 53%, respectively, in females. Adverse clinical signs included rough hair coat and hypoactivity at doses of 50 mg/kg and greater.

Two definitive micronucleus trials were performed and mice were sacrificed at 24 hours after the final dose in the first trial and 48 hours after final dose administration in the second trial; animals treated with positive control were sacrificed at 24 and 48 hours after dosing in trials 1 and 2, respectively. Bone marrow erythrocytes were removed from the femur of five mice from each dose group/sex and two bone marrow smears were prepared for each mouse. A total of 2000 polychromatic erythrocytes (PCE) for each mouse were screened for micronuclei. The micronucleus frequency of each dose for each sex was calculated from the total number of micronucleated PCE in 10000 PCE pooled from five mice and compared with that of the vehicle control. Micronucleated NCE were evaluated during the screening of micronuclei in 2000 PCE for each mouse and the total number was estimated based upon PCE/NCE ratio. Bone marrow toxicity was evaluated by the PCE/NCE ratio which was determined by the number of NCE enumerated during scoring approximately the first 200 PCE in each mouse. A trial was considered to be valid if the micronucleus frequency in vehicle controls was in the normal range (0.08 to 0.5%); a significant increase of micronucleus frequency in the positive control group above the vehicle control group; and data were available from at least three mice from the vehicle and positive control groups and from each test article dose group. The test article was considered to have caused a positive response if the test article induces a statistically significant increase of micronucleus frequencies in PCE at two consecutive doses. Cyclophosphamide (50 and 30 mg/kg for Trial 1 and 2, respectively) was used as a positive control.

**Results:** There was no significant increase in micronucleus frequency at any dose in males or females. Clinical signs were observed in high-dose animals (rough hair coat). In trial one, dose-related bone marrow toxicity was observed (9, 12 and 33% decrease in PCE/NCE ratios in males and 11, 14 and 24% in females at the low-, mid- and high-doses, respectively). At 48 hours, bone marrow toxicity was noted in mid- and high-dose males and females (11-12% and 23-36% reduction in PCE/NCE ratio, respectively). Cyclophosphamide induced a 16-fold and 6-fold increase of micronucleus frequency over the vehicle controls in trials one and two, respectively. The results indicate that SCH 45581 was negative under the conditions of this micronucleus assay, in concurrence with the sponsor's conclusion. However, the high-dose of 40 mg/kg appears to be low, especially in females, since no significant toxicity was observed in the definitive trials and since mortality in females was observed only at doses of 100 mg/kg or greater in the dose-ranging trials.

#### OVERALL SUMMARY AND EVALUATION:

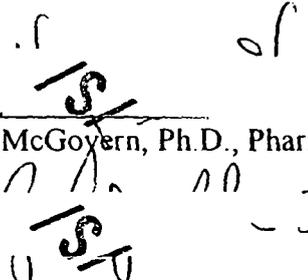
**Multiple Dose Toxicology:** A 3 month oral (dietary admixture) dose-ranging study in mice (24, 48, 96 and 192 mg/kg) was performed for the purpose of dose selection for a Phase 4, 2 year mouse carcinogenicity study. Drug-related mortality was observed in two high-dose males. Mean body weight gain was reduced by greater than 10% in the three highest dose-groups in males (high-dose males lost weight) and in high-dose females. The primary histological findings were

epididymides, heart, kidneys, liver, lungs, ovaries, seminal vesicles, stomach, spleen, thyroid, thymus, uterus, urinary bladder, and vagina. Histologic findings in the liver, lung, thymus and uterus were associated with significant changes in absolute or relative organ weight. Other significant findings included increased levels of BUN, AST, ALT and AP which were associated with histologic changes. In addition, induction of cytochrome P-450 in females and the enzymes EROD (2 highest doses) and PROD (3 lowest doses) as well as Cyp 2B1/2 (males and females) and Cyp 1A2 and P450 A (males only) were noted. An MTD of 48 mg/kg was identified in males and 96 mg/kg was selected in females. The toxicity profile is comparable to that observed previously in rats and monkeys.

**Genetic Toxicology:** An *in vivo* mouse bone marrow micronucleus assay and an Ames assay were performed with SCH 45581 (the 3-hydroxy metabolite of SCH 34117). Both assays were negative although high dose selection in the former study could likely have been increased. The results are consistent with the genotoxicity battery performed with SCH 34117.

### RECOMMENDATIONS

1. High doses of 48 mg/kg in males and 96 mg/kg in females in the 2 year mouse carcinogenicity study are recommended due to significant reductions in body weight gain and systemic findings of vacuolation and necrosis at the next higher doses in the 3 month dose-ranging study in mice.
2. The low and mid-doses in males should be lowered to 4 and 16 mg/kg, respectively, to provide an adequate dose response for the high dose. Similarly, the low and mid-doses in females should be increased to 10 and 32 mg/kg, respectively.
3. The above recommendations are pending the CAC's concurrence.

  
 Timothy J. McGovern, Ph.D., Pharmacologist

Addendum 1: Histopathology inventory for SCH 34117.

IND  
CC:

HFD-570/Division File  
 HFD-570/C.J. Sun  
 HFD-570/R. Nicklas  
 HFD-570/G. Trout  
 HFD-570/T.J. McGovern  
 HFD-540/B. Hill

7/28/2000  
July 28, 2000

**Addendum 1: Histopathology inventory for INU** \* Organ weight obtained

Study No.	P-6526	D18289	SN 98088	P-6973	P-6527	SN 98089	P-6976	SN 97253
Duration	14-day	14-day	28-day	3-month	14-day	28-day	3-month	3-month
Species	rat	rat	rat	Rat	monkey	monkey	monkey	mouse
Adrenals	X*		X*	X*	X*	X*	X*	X
Aorta	X		X	X	X	X	X	X
Bone marrow smear	X		X	X	X		X	X
Bone (femur)	X		X	X	X	X	X	X
Bone (rib)					X	X		
Bone (sternum)	X		X		X	X		
Brain:	X*		X*	X*	X*	X*	X*	X*
Cecum	X		X		X	X		
Cervix			X					
Colon	X		X		X	X		
Duodenum	X		X	X	X	X	X	
Epididymis	X*		X*	X*	X*	X	X*	X*
Esophagus	X		X	X	X	X	X	X
Eye	X		X	X	X	X	X	X
Fallopian tube								
Fat								
Gall bladder					X	X	X	X
Gross lesions	X	X			X	X	X	X
Harderian gland	X		X	X				X
Heart	X*		X*	X*	X*	X*	X*	X*
Hypophysis								
Ileum	X		X	X	X	X	X	
Injection site	NA	NA	NA		NA	NA		
Jejunum	X		X	X	X	X	X	
Kidneys	X*	X*	X*	X*	X*	X*	X*	X*
Lacrimal gland					X	X	X	
Larynx								
Liver	X*	X*	X*	X*	X*	X*	X*	X*
Lungs	X*	X*	X*	X*	X*	X*	X*	X*
Lymph nodes, cervical								X
Lymph nodes (LALN)				X			X	
Lymph nodes, mandibular	X		X		X	X		X
Lymph nodes, mediastinalis								
Lymph nodes, mesenteric	X		X		X	X		X
Mammary gland	X		X	X	X	X		X
Nasal cavity								
Optic nerves			X					
Ovaries	X*		X*	X*	X*	X*	X*	X*
Oviduct								
Pancreas	X	X	X	X	X	X	X	X
Parathyroid	X		X	X	X	X	X	X
Peripheral nerve				X				X
Pharynx								
Pituitary	X*		X*	X*	X*	X*	X*	X
Prostate	X*		X*	X*	X*	X*	X*	X
Rectum								
Salivary gland	X*		X*	X*	X*	X*	X*	X*
Sciatic nerve	X		X		X	X		
Seminal vesicles	X		X	X	X	X	X	X
Skeletal muscle	X		X	X	X	X	X	X
Skin	X		X	X	X	X	X	X
Spinal cord	X		X	X	X	X	X	X
Spleen	X*		X*	X*	X*	X*	X*	X*
Stomach	X		X	X	X	X	X	X
Testes	X*		X*	X*	X*	X*	X*	X*
Thoracic Limb	X							
Thymus	X*		X*	X*	X*	X*	X*	X*
Thyroid	X*		X*	X*	X*	X*	X*	X
Tongue	X		X	X	X	X	X	X
Trachea	X		X	X	X	X	X	X
Urinary bladder	X		X	X	X	X	X	X
Uterus	X*		X*	X*	X*	X*	X*	X*
Uterine horn								
Vagina	X		X	X	X	X	X	X

**DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS**  
**REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA**  
Chemistry Consult

**NDA No.** 21-165 **Date of Consult:** 20 OCT 1999

**Reviewer:** Timothy J. McGovern, Ph.D. **Review Completed:** 12 JUN 2000

**Information to be Conveyed to Sponsor:** Yes (✓), No ( )

**Sponsor:** Schering Plough Corp., Kenilworth, NJ

**Drug Name:** *Generic:* Descarboethoxyloratadine (DCL) ...  
*Code Name:* SCH 34117  
*Commercial:* undetermined

**Chemical name:** 5H-benzo[5,6]cyclohepta[1,2-b]pyridine, 8-chloro-6,11-(4-piperidinylidene)

**Formula:** C<sub>182</sub>H<sub>310</sub>N<sub>40</sub>O<sub>35</sub>

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**Molecular Weight:** 310.82

**Drug Class:** Anti-histamine

**Proposed Clinical Dose:** 5 mg/day, tablet

**Review:**

Dr. Kevin Swiss requested a safety assessment of two synthesis impurities in the desloratadine drug substance. The sponsor provided specifications for [ ] and [ ] (see figure 1) of not more than (NMT) [ ]% and [ ]%, respectively. The sponsor was requested in a letter dated March 20, 2000 (comment 7b) to tighten [ ] and [ ] in drug substance to less than 0.1%, or to qualify the proposed levels with suitable pharmacology/toxicology data. In response, the sponsor submitted to the NDA two 4-week toxicology studies in rats and monkeys in which [ ] and [ ] were added to SCH 34117 at a level of 0.3 and 0.5% in order to compare the toxicity profile with that of SCH 34117 alone. In addition, genotoxicity studies (Ames assay and chromosome aberration study) were performed using a SCH 34117 drug formulation with the same levels of [ ] and [ ]. [ ] is also found in loratadine 10 mg tablets (SCH 38598) with specifications set at NMT [ ]%. A safety assessment is provided for each of the degradation products.

[ ] The sponsor proposes that the specification for [ ] in the SCH 34117 drug substance be NMT [ ]% which exceeds the ICH Guidance for Industry Q3A recommendation of NMT 0.1% or 1 mg TDI without qualification. A structural alert for this impurity was identified since it is a [ ]. However, the reviewing chemist indicates that the activity would be [ ]

In addition, the sponsor submitted 4-week toxicology studies in rats and monkeys in which [redacted] was added to SCH 34117 at a level higher than that proposed in order to compare the toxicity profile with that of SCH 34117 alone. In addition, genotoxicity studies (Ames assay and chromosome aberration study) were performed using the SCH 34117 drug formulation with [redacted]

[redacted] (with a N-COOEt group; SCH 38597) has previously been approved at a level of NMT [redacted] % in loratadine 10 mg tablets. However, this level was approved prior to the publishing of the ICH Guidance for Industry Q3A and no qualification for this level of drug substance impurity was performed. Although the sponsor submitted two 4-week toxicity studies, qualification of impurities for drugs indicated for chronic use should be of 3 months duration. Currently submitted studies assessing SCH 34117 with added [redacted] did not produce genotoxicity under conditions tested. Although these studies further alleviate concern for genotoxicity, it should be noted that qualification of impurities should preferably utilize the impurities alone. Thus, the sponsor should limit the level of [redacted] in the drug substance to NMT 0.1% or provide qualification for [redacted] with a 3-month toxicity study. Further assessment of genotoxicity potential is not requested at this time due to the apparent weakness in structural activity and the negative findings in the studies submitted by the sponsor.

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The sponsor proposes that the specification for [redacted] in the SCH 34117 drug substance be NMT [redacted] % which exceeds the ICH Guidance for Industry Q3A recommendation of NMT 0.1% without qualification. The impurity [redacted] of SCH 34117 and structural alerts have not been identified.

As stated previously, the sponsor submitted 4-week toxicology studies in rats and monkeys in which [redacted] had been added to SCH 34117 at a level of [redacted] % in order to compare the toxicity profile with that of SCH 34117 alone. In addition, genotoxicity studies (Ames assay and chromosome aberration study) were performed using a SCH 34117 drug formulation with the same level of [redacted]. Under the same rationale used for impurity [redacted] the sponsor should limit the level of [redacted] in the drug substance to NMT 0.1% or provide qualification for [redacted] with a 3-month toxicity study.

**Overall Summary and Evaluation:** A safety assessment was performed for two drug substance impurities [redacted]. The sponsor proposed specifications of NMT [redacted] % and [redacted] % for [redacted] and [redacted] respectively, and submitted 4-week toxicity studies in rats and monkeys and two genotoxicity studies in which the impurities were added to the SCH 34117 drug formulation at levels slightly greater than those proposed. Toxicity studies performed for qualification of impurities for drugs indicated for chronic use should be of 3 months duration. Thus, the sponsor should limit the levels of [redacted] and [redacted] to NMT 0.1% in the drug substance or provide further qualification for the drug substance impurities. Concerns for genotoxicity of [redacted] are alleviated by the weak structural activity of the molecule and the negative findings in the studies submitted by the sponsor.

**RECOMMENDATION**

The sponsor should limit the levels of [ ] and [ ] to NMT 0.1% in the drug substance or provide further qualification for the drug substance impurities (3 month toxicity study using appropriate levels of impurities).

*TS*  
\_\_\_\_\_  
Timothy J. McGovern, Ph.D., Pharmacologist  
*TS*

*June 12, 2000*

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HFD-570/C.J. Sun  
HFD-570/K. Swiss  
HFD-570/G. Trout  
HFD-570/T.J. McGovern  
*HFD-540/B. Hill*

*JUNE 12, 2000*



The following table summarizes the studies submitted and reviewed in this document:

**Preclinical Studies Submitted and Reviewed in this IND:**

Study	Report #	Serial #
<b>Safety Pharmacology:</b>		
Effect of loratadine and its metabolite, descarboethoxyloratadine, on the QT interval in the isolated perfused rabbit heart model (Langendorff)	30523	051
Effect of IN-0133 on electrophysiological and mechanical properties of guinea pig ventricular muscle	30416	051
Effects of IN 0132 on the Na <sup>+</sup> current in rabbit ventricular myocytes	30417	051
Report on the effect of IN-0132, IN-0133, 0049 and IN-0057 on two K currents, iKr and iKl in rabbit ventricular myocytes	30148	051
<b>Pharmacokinetics:</b>		
SCH 34117: A study of the tissue distribution of radioactivity in male and female sprague dawley rats and male rats following a single oral dose of <sup>14</sup> C-SCH 34117	P-6741	094

**Studies Not Reviewed in this IND:**

**Studies Previously Reviewed: None**

*Note: Portions of this review were excerpted directly from the sponsor's submission.*

**SAFETY PHARMACOLOGY:** The sponsor submitted four reports which assessed the comparative potential to induce adverse cardiac events of SCH 34117 and loratadine; results of these studies are summarized in Table 1. SCH 34117 increased QT interval (up to 41% at 10 μM) in a dose- and time-dependent manner in isolated rabbit hearts, primarily due to increasing the QRS complex (up to 5-6-fold at 10 μM). SCH 34117 alone did not affect JT interval but enhanced a quinidine-induced increase. Loratadine had no effects on QT, QRS or JT intervals at concentrations up to 50 μM. In isolated perfused guinea pig left ventricular papillary muscle, SCH 34117 decreased V<sub>max</sub> and velocity of impulse conduction and increased excitation threshold (≥ 30 μM) while producing a negative inotropic effect (10 μM). No effect was noted on resting potential or action potential duration up to 100 μM. In isolated rabbit ventricular myocytes, SCH 34117 (100 μM) reduced Na<sup>+</sup> current more effectively than 100 μM loratadine; loratadine showed preferential binding to channel in inactivated state. Other effects included reduced delayed rectifier current (iKr) to ~ 1/2 control value at 6 x 10<sup>-6</sup> M as the concentration at

which  $\frac{1}{2}$  current is blocked ( $k_{0.5}$ ) was  $5 \times 10^{-6}$  M ( $k_{0.5}$  for loratadine was  $8.7 \times 10^{-6}$ ). SCH 34117 had no effect at  $10^{-5}$  M on inward rectifier current ( $i_{K1}$ ) although the curve was flatter at  $3 \times 10^{-5}$  M; loratadine had more pronounced effect than SCH 34117. Thus, SCH 34117 exerted effects on various cardiac parameters at concentrations ranging from 5-100  $\mu$ M.

**Table 1.** Safety pharmacology studies demonstrating cardiac effects of SCH 34117.

Parameter/Model	Activity
Isolated, perfused rabbit hearts	<p>SCH 34117: increased QT interval (15% and 41% at 5 <math>\mu</math>M and 10 <math>\mu</math>M, respectively, after 30 minutes); experiments prematurely terminated after 50 <math>\mu</math>M due to sustained ventricular fibrillation; NOEL = 1 <math>\mu</math>M.</p> <p>QT increase at 10 <math>\mu</math>M increased through first 100 minutes; could not be measured after 2 hours due to flattening of T wave;</p> <p>QRS interval increased 5 to 6-fold at 10 <math>\mu</math>M 2 hours after dosing; increased up to 34% at 0.5 <math>\mu</math>M after 3 hours; NOEL = 0.2 <math>\mu</math>M.</p> <p>No effect of SCH 34117 alone on JT interval. Produced nearly two-fold increase in JT interval at 0.5 <math>\mu</math>M in combination with quinidine compared to quinidine alone (15%).</p> <p>Loratadine (up to 50 <math>\mu</math>M) had no effect on QT, QRS or JT intervals</p>
Perfused guinea pig left ventricular papillary muscle	<p><b>Remark: Drug listed in report as IN-0133, assumed to be SCH 34117.</b></p> <p>No effect on resting potential or action potential duration at drug concentration of 10, 30 or 100 <math>\mu</math>M.</p> <p>SCH 34117 decreased <math>V_{max}</math> at <math>\geq 30</math> <math>\mu</math>M with pacing at 1 Hz; decrease of 57% at 100 <math>\mu</math>M. Associated with decrease in velocity of impulse conduction and increase in excitation threshold. Decrease in <math>V_{max}</math> enhanced at higher pacing frequencies. Full reversibility not obtained up to 2 hrs.</p> <p>Negative inotropic effect in 4 of 5 preparations at 10 <math>\mu</math>M (decreased isometric force to 70% of pre-drug level at 1 Hz).</p>
Isolated rabbit ventricular myocytes	<p><b>Remark: Drug listed in report as IN-0133, assumed to be SCH 34117.</b></p> <p><b>Drug listed in report as IN 0132, assumed to be Loratadine.</b></p> <p>Effects on <math>Na^+</math> current: SCH 34117 (100 <math>\mu</math>M; 5-10 min) reduced <math>Na^+</math> current at holding potentials of -100 to -80 mV more effectively than 100 <math>\mu</math>M loratadine. Loratadine showed preferential binding to channel in inactivated state.</p> <p>Effects on delayed rectifier current (<math>i_{Kr}</math>): SCH 34117 (<math>6 \times 10^{-6}</math> M) reduced <math>i_{Kr}</math> current to <math>\sim \frac{1}{2}</math> control value at 10 mV. Only small remnant of <math>i_{Kr}</math> current visible at <math>3 \times 10^{-5}</math> M. Concentration at which <math>\frac{1}{2}</math> current is blocked (<math>k_{0.5}</math>) = <math>5 \times 10^{-6}</math> M. <math>k_{0.5}</math> for loratadine = <math>8.7 \times 10^{-6}</math> M</p> <p>Effect on inward rectifier current (<math>i_{K1}</math>): no effect at <math>10^{-5}</math> M; IV curve flatter at <math>3 \times 10^{-5}</math> M. Loratadine had more pronounced effect than SCH 34117 and was more slowly reversible.</p>

**PHARMACOKINETICS AND TOXICOKINETICS:**

Pharmacokinetic parameters in rats following oral (gavage) administration are summarized in Table 2. The C<sub>max</sub> and AUC for total radioactivity were 1.5-1.8 times higher in males. Plasma concentrations of unchanged drug at 3 hours were 2.6 times higher in females than in males. The plasma concentrations < LOQ ( ng/ml) by 24 hours in males and 72 hours in females. The AUC for SCH 34117 was not calculated since the concentration fell below the LOQ before adequate elimination phase could be described.

**Table 2.** PK values following single oral dose of SCH 34117 (6.5 mg/kg) in SD rats.

Parameter	Males	Females
	Drug-derived radioactivity	
C <sub>max</sub> (µg equiv/g)	0.648	0.426
T <sub>max</sub> (hr)	6	3
AUC(tf) (µg equiv.hr/g)	13.9	7.65
	SCH 34117	
C <sub>max</sub> (µg/ml)	0.0995	0.259
T <sub>max</sub> (hr)	3	3
AUC(tf) (µg equiv.hr/g)	Not calculated	Not calculated

~~Previously submitted 14-day and 3-month studies in rats have demonstrated similar findings at comparable doses including increased SCH 34117 exposure in females.~~

**Distribution:** Table 3 summarizes the tissue distribution of a single oral (gavage) dose of <sup>14</sup>C-SCH 34117 (6.5 mg/kg) in Sprague Dawley rats. In males, tissues (excluding GI tract) with the highest concentrations of radioactivity (6 hours) were the pituitary, adrenal gland, lung, liver, and mesenteric lymph nodes. At 168 hr post-dose the concentration of radioactivity in most tissues was about 1- to 12-fold greater than those in plasma and the tissue to plasma ratios were generally higher than those at 6 hours. At 672 hours post-dose 0.071% of administered dose was in collected tissues and only thyroid had notable concentrations (consistent with loratadine studies). Females were similar to males in terms of tissue distribution and brown fat, peritoneal fat kidneys and thyroid concentrations were higher than plasma at 168 hours and only 0.002% of administered dose was noted in collected tissues. The tissues with lowest concentrations were the plasma, brain, blood, eyes, spinal cord, and testes. The results suggest a greater penetration of drug-derived radioactivity into tissues in female rats compared to males as mean plasma concentrations were 2- to 4-fold higher from 1 to 6 hours and radioactivity concentrations in many tissues in females at 1, 3 and 6 hours post-dose were approximately 1.5- to 2.5-fold greater in comparison to males.

**Table 3.** Tissue distribution of  $^{14}\text{C}$ -SCH 34117 in rats after single oral gavage administration.

Tissue	Males (6 hrs)		Females (3 hrs)	
	Total radioactivity ( $\mu\text{g equiv/g}$ )	Tissue:Plasma ratio	Total radioactivity ( $\mu\text{g equiv/g}$ )	Radioactivity in peptide fraction
Plasma	0.648	1	0.426	1
Adrenal gland	17.7	27.2	30.2	70.9
Harderian gland	10.2	15.7	11.7	27.5
Kidney	7.90	12.2	13.3	31.2
Liver	15.4	23.8	20	46.9
Lungs	15.5	23.9	28.4	66.7
Mes. Lymph nodes	12	18.5	11.9	27.9
Pituitary	30.4	46.9	31.8	74.6
Spleen	8.17	12.6	14.7	34.5
Thyroid	8.44	13	14.3	33.6

In male Long Evans rat there was no difference in binding of radioactivity to pigmented or non-pigmented skin following a single oral gavage dose (6.5 mg/kg; Table 4). The eye had concentrations ranging from to  $\mu\text{g equiv/g}$  which declined slowly and were still detectable at 672 hours. The highest concentrations were detected in the liver and kidneys.

**Table 4.** Tissue distribution in male Long Evans rats after single oral gavage administration.

Tissue	Males (3 hrs)	
	Total radioactivity ( $\mu\text{g equiv/g}$ )	Tissue:Plasma ratio
Plasma	0.795	
Blood	0.875	1.1
Eyes (pigmented)	3.57	4.49
Kidney	9.27	11.7
Liver	26	32.7
Skin (non-pigmented)	1.58	1.99
Skin (pigmented)	1.72	2.16

**Excretion:** Following a single oral dose of  $^{14}\text{C}$ -SCH 34117 to Sprague Dawley rats, 98 and 95% of administered radioactivity was recovered by 168 hours from males and females, respectively. 69-70% of the dose was recovered in feces while 25-27% was eliminated in urine. Negligible amounts were recovered in cage wash and as  $\text{CO}_2$  (0.06-0.36%).

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## OVERALL SUMMARY AND EVALUATION

**Safety Pharmacology:** SCH 34117 dose- and time-dependently increased QT interval (up to 41% at 10  $\mu$ M) in isolated rabbit hearts, due primarily to increasing the QRS complex up to 5-6-fold. SCH 34117 did not increase JT interval alone but did enhance a quinidine-induced increase. Loratadine had no effects on QT, QRS or JT intervals at up to 50  $\mu$ M. SCH 34117 also decreased Vmax and velocity of impulse conduction and increased excitation threshold ( $\geq 30$   $\mu$ M) while producing a negative inotropic effect (10  $\mu$ M) in isolated perfused guinea pig left ventricular papillary muscle. No effect was noted on resting potential or action potential duration up to 100  $\mu$ M. In isolated rabbit ventricular myocytes, SCH 34117 (100  $\mu$ M) reduced Na<sup>+</sup> current more effectively than 100  $\mu$ M loratadine; loratadine showed preferential binding to channel in inactivated state. Other effects included reduced delayed rectifier current (iKr) current to  $\sim 1/2$  control value at  $6 \times 10^{-6}$  M as the concentration at which  $1/2$  current is blocked (k0.5) was  $5 \times 10^{-6}$  M (k0.5 for loratadine was  $8.7 \times 10^{-6}$ ). SCH 34117 had no effect at  $10^{-5}$  M on inward rectifier current (iK1) although the curve was flatter at  $3 \times 10^{-5}$  M; loratadine had more pronounced effect than SCH 34117. Thus, SCH 34117 exerted effects on various cardiac parameters in vitro at concentrations ranging from  $\mu$ M. SCH 34117 was previously shown to have less or equal potency compared to loratadine in inhibiting rat and guinea pig cardiac K<sup>+</sup> channels as well as a cloned human hKv1.5. All findings were observed during in vitro assessments while in vivo studies in monkeys for up to 3 months produced no drug-related effects on cardiac parameters. In addition, the absence of loratadine-induced adverse cardiac effects in humans suggests that SCH 34117 is reasonably safe in this regard. A previous consult with Dr. Peter Honig, acting Medical Officer, concluded that no further preclinical assessment of cardiovascular effects is necessary.

**Pharmacokinetics:** The Cmax and AUC for total radioactivity following oral gavage administration were 1.5-1.8 times higher in males compared to females. However, plasma concentrations of unchanged drug was 2.6 times greater in females at 3 hours after dosing. Plasma concentrations were less than the LOQ by 24 hours in male and 72 hours in female. Tissue distribution of a single oral (gavage) dose of <sup>14</sup>C-SCH 34117 in Sprague Dawley rats was observed primarily in the pituitary, adrenal gland, lung, liver, spleen and mesenteric lymph nodes. At 168 hr post-dose the concentration of radioactivity in most tissues was about 1- to 12-fold greater than those in plasma and the tissue to plasma ratios were generally higher than those at 6 hours. At 672 hours post-dose 0.071% of administered dose was in collected tissues and only thyroid had notable concentrations (consistent with loratadine studies). The results suggest a greater penetration of drug-derived radioactivity into tissues in female rats compared to males as mean plasma concentrations were 2- to 4-fold higher from 1 to 6 hours and radioactivity concentrations in many tissues in females at 1, 3 and 6 hours post-dose were approximately 1.5- to 2.5-fold greater in comparison to males. Tissue distribution of SCH 34117 is comparable to that observed during the loratadine development program. No difference in tissue distribution to pigmented or non-pigmented skin was noted in male Long Evans rats although radioactivity was detected in the eye. A single oral gavage dose of <sup>14</sup>C-SCH 34117 was excreted primarily in feces.

RECOMMENDATION

None at this time.

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1/5/1  
6/7/00  
Timothy J. McGovern, Ph.D., Pharmacologist  
7, 2000

Original IND [ ]  
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HFD-570/T.J. McGovern  
HFD-540/B. Hill

**HFD-570 : DIVISION OF PULMONARY DRUG PRODUCTS  
REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA  
Review #4**

IND No. [       ]	Serial No.	048	Submission Date:	01 APR 1999
		075		13 AUG 1999
		084		17 SEP 1999
		088		05 OCT 1999

Reviewer: Timothy J. McGovern, Ph.D.

Review Completed: 31 JAN 2000

Information to be Conveyed to Sponsor: Yes (✓), No ( )

Sponsor: Schering-Plough Corporation

Drug Names: Descarboethoxyloratadine (DCL) Code Name: SCH 34117

Class: Anti-histamine

~~Indication: Allergic rhinitis/~~

Route of Administration: Oral (tablet)

Proposed Clinical Protocols: None with these submissions.

Previous Clinical Experience: Phase I and Phase II studies in both healthy volunteers and patients with seasonal allergic rhinitis.

**Previous Review(s), Date(s) and Reviewer(s):**

<u>Review Type</u>	<u>Date of Submission(s)</u>	<u>Reviewer</u>	<u>Date of Review</u>
Original Review	March 9, 1998	McGovern	May 22, 1998
Review #2	July 8-October 19, 1998	McGovern	October 27, 1998
Review #3	November 23, 1998	McGovern	December 15, 1998

**Background:** The submission of Serial No 048 contains summary reports of 3-month oral (gavage) toxicity studies in rats and monkeys (Study # P-6973 and P-6976, respectively). The sponsor previously submitted draft tables of clinical observations and gross findings from a 3-month monkey study (Serial No 032) in order to gain Agency concurrence on the Sponsor's plan not to perform an additional 3-month study in monkeys to fulfill bridging requirements to the chronic studies performed in the development program for loratadine. The sponsor was informed that a final decision on this issue must await submission of the histopathology and PK/TK data

from the 3-month monkey study (see Review #3). The sponsor's intent with the current submissions is to submit supporting toxicology information for planned chronic idiopathic urticaria trials which will be six weeks in duration and are planned to start in late April, 1999, to support bridging to the chronic toxicology program performed with loratadine and to obtain a waiver for carcinogenicity studies assessing SCH 34117. Currently, trials up to 4 weeks in duration have been performed based upon summary reports of 4-week toxicology studies in rats and monkeys. A Pre-NDA meeting was held May 11, 1999 to discuss, among other issues, the use of the 3-month studies to bridge to the chronic loratadine development program. Submission 075 contains the sponsor's request for a waiver from performing carcinogenicity studies in support of the desloratadine bridging strategy and includes the in vivo mouse micronucleus assay. Submission 088 includes additional information in support of the carcinogenicity waiver request. Submission 084 includes the final 3-month toxicology study reports including toxicokinetic data.

The issue regarding the carcinogenicity waiver request was addressed by the Senior Pharmacology/Toxicology Policy Group on September 14, 1999. The background packages provided to the Policy Group and the minutes of the Policy Group meeting are included as Attachments 1, 2 and 3 at the end of this review. See the minutes of the Policy Group meeting for the final recommendations regarding the sponsor's waiver request.

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The following table summarizes the studies submitted in these submissions:

**Preclinical Studies Submitted and Reviewed in this IND:**

Study	Report #	Serial #	Volume
<i>Multiple Dose Toxicology:</i>			
Summary report of 3-mos oral (gavage) rat toxicology study	P-6973	048	12.1
Summary report of 3-mos oral (gavage) monkey toxicology study	P-6976	048	12.2
Final report of 3-mos oral (gavage) rat toxicology study	P-6973	084	23.1
Final report of 3-mos oral (gavage) monkey toxicology study	P-6976	084	23.4
<i>Genetic Toxicology:</i>			
Mouse bone marrow erythrocyte micronucleus study of SCH 34117	P6912	075	21.7

**Studies Not Reviewed in this IND:** None.

**Studies Previously Reviewed:** None

*Note: Portions of this review were excerpted directly from the sponsor's submission.*

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## TOXICOLOGY

## MULTIPLE-DOSE TOXICITY:

## Rat, 3-Month Oral (Gavage) Toxicity

Doc. No.: P-6973 [ Study No.: [ Sponsor Study No.: 97016 Vol.: 23.1

Study Dates: Starting date: 3/9/1998; summary report issued: 7/1999

Testing Lab: [ ]

Test Article: SCH 34117 (Batch 97-34117-X-03-RA; purity not reported) in 0.4% methylcellulose; SCH 29851 (Batch MI-A-00851; purity not reported)

Concentration: 0.6-24 mg/ml.

Dose Volume: 5 ml/kg.

GLP: This report included a signed GLP report.

QA report: Yes.

**Methods:** Sprague-Dawley rats (5-7 weeks old, 169-291 g) were assigned to the following treatment groups:

Dose (mg SCH 34117/kg/day):	Veh. Control	3	30	60	120	120 mg loratadine/kg/day
No./sex	10	10	10	10	10	10

Each rat received a daily dose of vehicle, test drug or comparative dose of loratadine by oral (gavage) administration for 3 months. The following observations were made:

Clinical observation . . . assessed daily  
 Body weight . . . . . weekly  
 Food consumption . . . . . weekly  
 Water consumption . . . . . not assessed  
 Health exam . . . . . not assessed  
 Ophthalmoscopy . . . . . pre-test and Week 12; left eye only  
 ECG . . . . . not assessed  
 Hematology . . . . . Weeks 4 and 13  
 Clinical chemistry . . . . . Weeks 4 and 13  
 Urinalysis . . . . . Weeks 4 and 13  
 Enzyme induction . . . . . Liver samples assayed for protein content, cytochrome P450 content, 7-pentoxoresorufin O-dealkylase (PROD) activity and 7-ethoxyresorufin O-dealkylase (EROD)  
 Organ weights . . . . . at sacrifice (for specific tissues/organs see Addendum, page 32)  
 Gross pathology . . . . . at sacrifice  
 Histopathology . . . . . at sacrifice, all tissues were examined in the control (vehicle and comparative) high-mid-dose and high-dose rats (for specific tissues/organs see Addendum, page 32). Target organs were evaluated to the no-effect level in the low- and low-mid-dose groups.

ics . . . . . blood samples obtained from 2 rats/sex/group/time point from the dosed rats at approximate times of 1, 2.5, 4, 8, 12 and 24 hours after dosing on Days 1 and during week 9.

**Results:**

*Mortality:* Mortality was noted following blood collection on Day 1 in all groups except for the low-dose group; vehicle control animals were not bled. The animals that died were replaced. Treatment-related mortality was noted in high-dose males (9 of 10, Days 19-63), in females at doses  $\geq 30$  mg/kg DCL (lower-middle-dose: 2 of 10, days 41 and 68; upper-middle-dose: 6 of 10, days 9-63; high-dose: 10 of 10, days 19-36) and in comparative controls (6 of 10, days 23-87).

**Table 1: Total incidence of mortality.**

Dose (mg SCH 34117/kg/day):	0	3	30	60	120	120 mg loratadine/kg/day
Males	0	0	0	0	9	0
Females	0	0	2	6	10	6

*Clinical Observations:* Anti-cholinergic effects were the primary drug-related clinical observations in this study (Table 2). These included enlarged, few or no feces in animals administered doses of  $\geq 30$  mg/kg SCH 34117 and loratadine-treated animals. Increases in the incidence of hypothermia, lethargy, paleness, rough coat, extended abdomen, thin appearance, ataxia, labored respiration/respiratory sounds, wet urogenital region and hunched posture were also noted in these groups. The incidence in the loratadine-control group showed greater similarity to the 60 mg/kg SCH 34117 group than the 120 mg/kg SCH 34117 group, likely due to differences in systemic exposure to SCH 34117.

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**Table 2.** Clinical observations in rats following 3-month administration.

Observation	Females						Males						
	Dose (mg/kg)	0	3	30	60	120	120 - Lor	0	3	30	60	120	120 - Lor
Feces - few		0	0	8	10	10	10	0	1	1	10	10	7
Feces - none		0	0	0	1	0	3	0	0	0		1	1
Feces - enlarged		0	0	10	9	10	10	0	0	10	10	10	10
Hunched posture		0	0	0	6	10	10	0	1	0	1	10	1
Hypothermic		0	0	0	0	6	0	0	0	0	1	5	0
Lethargic		0	0	0	3	9	2	0	0	0	1	4	3
Pale		0	0	1	7	10	7	0	0	0	1	7	1
Rough coat		0	0	3	9	10	9	0	1	0	1	9	1
Thin appearance		0	1	5	10	10	10	0	1	0	1	8	2
Ataxic		0	0	0	0	1	0	0	0	0	1	2	1
Convulsive		0	0	0	1	0	0	0	0	0	0	1	0
Labored respiration		0	0	2	5	9	5	0	0	1	2	6	0
Nasal discharge - red		0	0	0	0	0	5	0	1	0	2	6	0
Respiratory sounds - rales		0	0	2	3	3	0	0	1	1	0	4	1
Swollen abdomen		0	0	0	0	0	2	0	0	0	0	2	0
Urogenital region - wet		0	0	1	1	7	2	0	0	0	0	1	0

**Body Weight:** Body weight gain was significantly reduced in upper-mid and high-dose males and females administered  $\geq 30$  mg/kg (Table 3). In males, significant reductions in the upper-mid and high-dose groups were observed from Days 29 and 8, respectively. In females, significant reductions in the lower-mid, upper-mid and high-dose groups were observed from Days 43, 22 and 36, respectively. The active control groups were also reduced (from Days 22 in males and 29 in females) and were comparable to the upper-mid-dose DCL groups.

**Table 3:** Change in body weight gain following 3-months treatment.

Dose (mg SCH 34117/kg/day):	3	30	60	120	120 mg Lor/kg/day
<b>Males</b>					
% $\Delta$ from control	↓1	↓12	↓33	↓99*	↓50
<b>Females</b>					
% $\Delta$ from control	↓7	↓33	↓73	↓139**	↓62

\*: Day 54.

\*\* : Day 36.

**Food consumption:** Food consumption was reduced in male rats administered 60 or 120 mg/kg SCH 34117 beginning on Day 8. The statistically significant reduction in the high dose group (36-54%) was continuous, while that in the 60 mg/kg group was intermittent, ranging from 22% at Day 8 to 9-12% on Days 78-91. Significant reductions in active control males were noted only on Days 8 and 57 (16 and 19%, respectively). Females were more significantly affected as reductions were consistently reported in the same three groups from Day 8 onward. Reductions ranged from 24-32% in the 60 mg/kg group, 36-75% in the 120 mg SCH 34117/kg group, and 13-36% in the loratadine treatment group.

*Ophthalmoscopy:* No treatment-related findings were reported.

*Hematology:* The high-dose SCH 34117 groups could be assessed only at Day 23 due to high mortality. Significant, but small, increases in erythrocyte, hemoglobin and hematocrit levels were noted (Table 4). In addition, total leukocyte counts were reduced and platelet counts were increased. WBC differentiation demonstrated reduced lymphocytes and eosinophils. At day 92, findings included a slight reduction in mean corpuscular hemoglobin concentration in active male controls, increased erythrocyte hemoglobin, and increased hematocrit in the two mid-dose female groups and the female active control group. Monocyte reductions were also noted in upper-mid dose and active control males, while prothrombin and activated partial prothrombin time were reduced in males, but increased in females.

**Table 4.** Hematologic findings in rats following 3-month administration.

Hematology	Males						Females						
	Dose (mg/kg)						Dose (mg/kg)						
	0	3	30	60	120*	120 - L	0	3	30	60	120*	120 - L	
Leukocyte													
% Δ from control		↑4	↓4	↑5	↓32	↓7		↑14	0	↑17	↓25	↓13	
Erythrocyte													
% Δ from control		↑4	↑2	0	↑16	↑1		↑2	↑10	↑12	↑10	↑13	
Hemoglobin													
% Δ from control		↑1	↑2	↓1	↑12	↓3		↑2	↑10	↑11	↑7	↑7	
Hematocrit %													
% Δ from control		↑2	↑2	↑1	↑12	0		↑2	↑10	↑12	↑6	↑11	
Platelets													
% Δ from control		0	↓14	↑7	↑32	↓1		↓2	↓12	↑8	↑51	↑15	
Lymphocytes													
% Δ from control		↑2	0	↑4	↓49	↑6		↑10	↑1	↓5	↓67	↓27	
Monocytes													
% Δ from control		↑7	↓64	↓66	↑147	↓70		↑48	↓71	↑176	↑8	↓33	
Eosinophils													
% Δ from control		0	↓15	↓20	↓69	↓40		↑38	↓15	↓54	↓79	↓46	
Neutrophils													
% Δ from control		↑9	↓4	↑36	↑50	↑50		↑48	↑16	↑170	↑377	↑115	
Prothrombin time (seconds)	13	13	12	12	13	11.5	11	11	10.9	11		11.5	
APTT (seconds)	12	11	9.7	9.6	9.9	9.4	10	10	9.8	11		11	

Shaded areas indicate statistically significant difference from control group (p < 0.05).

\* Day 23.

*Clinical Chemistry:* The high-dose SCH 34117 groups were only assessed on Day 23 due to high mortality. Drug-related findings are summarized in Table 5 and include slight alterations in albumin, increases in cholesterol, globulin, and total protein. Aspartate aminotransferase, alanine aminotransferase and BUN were also increased 2.5 to 5-fold, 1 to 2-fold, and 1.5 to 2-fold, respectively, in males and females, while A/G ratio, glucose, and triglycerides were slightly to moderately reduced.

**Table 5. Clinical chemistry findings in rats following 3-month administration.**

Clinical chemistry	Males					Females				
	Dose group (mg/kg)					Dose group (mg/kg)				
	3	30	60	120*	120-L	3	30	60	120*	120-L
Albumin % Δ from control	↑5	↑11	↑11	↓12	↑16	↑6	↑4	↓14	↓17	↓12
Cholesterol % Δ from control	↑12	↑26	↑46	↑69	↑12	↑11	↑21	↑66	↑24	↑124
Globulin % Δ from control	no Δ	↑9	↑23	↑15	↑27	↑10	↑15	↑15	↓12	↑35
Total protein % Δ from control	↑5	↑12	↑17	↓3	↑22	↑7	↑7	↓7	↓15	↑1
Aspartate aminotrans % Δ from control	↑2	↓11	↓14	↑489	↓14	↑2	↑22	↑60	↑250	↑32
Alanine aminotrans % Δ from control	↑8	↑11	↑14	↑231	↑25	↑37	↑39	↑16	↑103	↓20
AG ratio % Δ from control	↑2	↓1	↓15	↓21	↓13	↓5	↓8	↓24	↓1	↓37
Glucose % Δ from control	↓6	↓6	↓10	↓51	no Δ	↓5	↓10	↓16	10	↓12
Triglycerides % Δ from control	↑17	↓22	↓72	↓65	↓74	↑10	↑21	↑74	↓51	↓50
BUN % Δ from control	↓7	no Δ	no Δ	↑159	↑14	no Δ	↓6	↑81	↑207	↑88

Shaded areas indicate statistically significant difference from control group ( $p < 0.05$ ).

120-L: 120 mg/kg loratadine active control group.

\* Day 23.

**Enzyme Induction:** Liver weight, liver to body weight ratio and microsomal protein content were all increased in male rats administered 30 and 60 mg/kg SCH 34117 and 120 mg/kg loratadine (Table 6). The high-dose SCH 34117 groups were not assessed due to the high incidence of mortality. These findings were consistent only in the female active control group. In addition, cytochrome P450 induction was greater in females while induction of PROD was greater in males. Responses tended to be greater in the active control animals compared to the animals administered 60 mg/kg SCH 34117.

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**Table 6.** Enzyme induction in rats following 3-month drug administration.

Dose (mg/kg/d)	Males					Females				
	0	3	30	60	120-L	0	3	30	60	120-L
<b>Liver weight</b>										
% Δ from control		↓1	↑40	↑39	↑79	↓1	↓9	↑1		↑62
<b>Liver/Body wt ratio</b>										
% Δ from control		no Δ	↑41	↑67	↑111	↑7	↑7	↑41		↑115
<b>Microsomal protein (mg/tot liver)</b>										
% Δ from control		↑21	↑98	↑71	↑102	↓4	↑15	↑36		↑172
<b>Cytochrome P450</b>										
% Δ from control						no Δ	↑15	↑47		↑94
Nmol/mg microsomal protein		↓6	↑7	↑9	↑13					
Nmol/g liver		↑13	↑52	↑38	↑29	↓8	↑41	↑88		↑215
Nmol/total liver		↑11	↑110	↑86	↑129	↓8	↑31	↑89		↑403
<b>Enzyme Induction</b>										
% Δ from control										
<b>PROD</b>										
pmol/min/mg micros. protein		↓5	↑688	↑140	↑233	↑6	↑232	↑97		↑15
pmol/min/g liver		↑17	↑1053	↑210	↑287	no Δ	↑310	↑110		↑86
pmol/min/total liver		↑19	↑1568	↑332	↑615	↓1	↑275	↑107		↑198
<b>EROD</b>										
pmol/min/mg micros. protein		↓37	↓16	↓51	↓49	↓12	↑32	↑14		↑11
pmol/min/g liver		↓28	↑2	↓41	↓45	↓19	↑57	↑44		↑76
pmol/min/total liver		↓28	↑47	↓20	↓3	↓21	↑44	↑41		↑176

Shaded areas indicate a significant difference from vehicle controls.

**Urinalysis:** Urine volumes were increased in loratadine-treated animals and in males administered the mid-doses after 3 months treatment (Table 7). In addition, urine osmolarity was reduced in the same groups. Results in the high-dose DCL group were not consistent and may be due to the earlier sampling time for this group.

**Table 7.** Urinalysis results in rats following 3-month administration.

Urinalysis	Males					Females				
	Dose group (mg/kg)					Dose group (mg/kg)				
	3	30	60	120*	120-L	3	30	60	120*	120-L
<b>4-hour volume</b>										
% Δ from control	28	35	11	39	44	-10	20	66	3	39
<b>24-hour volume</b>										
% Δ from control	13	87	53	-19	62	-2	21	20	20	99
<b>Osmolarity</b>										
% Δ from control	-17	51	43	6	55	8	-17	56	-18	43

Shaded areas indicate statistically significant difference from control group (p < 0.05).

120-L: 120 mg/kg loratadine active control group.

\* Day 22/23.

**Organ Weight:** The high-dose female desloratadine group was not assessed due to high mortality and only one high-dose male was assessed. Findings from the other dose groups demonstrated increases in liver, lung, adrenal, heart and kidney weights, and decreases in spleen, thymus and

uterus weights (Table 8). The active control group was generally comparable to the mid-dose groups.

**Table 8.** Organ weight changes in rats following 3-month administration.

Organ weight	Males					Females				
	3	30	60	120	120-L	3	30	60	120	120-L
Dose group (mg/kg) n =	10	10	10	1	10	10	8	4	0	4
Liver										
AOW-% Δ from control	3	27	48	10	69	4	4	10		76
RTB	4	34	78	127	101	5	16	44		121
RTBr	6	31	53	15	73	1	5	15		87
Lungs										
AOW-% Δ from control	-11	20	44	40	22	10	68	130		105
RTB	-10	27	73	187	46	11	88	197		156
RTBr	-9	24	49	46	25	7	70	138		119
Spleen										
AOW-% Δ from control	-2	24	24	-52	17	-4	-18	30		-15
RTB	-1	19	8	-2	-1	-3	-9	-10		7
RTBr	1	21	21	-50	15	-7	-17	27		-10
Thymus										
AOW-% Δ from control	11	4	23	43	3	19	-11	31		36
RTB	10	3	-7	18	15	20	no Δ	-11		-20
RTBr	14	-1	-20	-40	-1	15	-11	-28		32
Uterus										
AOW-% Δ from control						32	22	-47		-51
RTB						33	35	-33		-38
RTBr						28	24	-45		-48
Adrenals										
AOW-% Δ from control	-3	-10	-11	41	-4	2	-6	11		13
RTB	-3	-6	7	188	14	2	5	45		44
RTBr	1	-7	-7	48	-1	-2	-5	15		20
Brain										
AOW-% Δ from control	-3	-3	-4	-4	-3	3	-1	-4		-6
RTB	-3	3	15	96	16	4	11	25		19
Heart										
AOW-% Δ from control	-3	-7	-11	-18	-9	4	-4	-7		-1
RTB	-3	-2	7	67	7	5	8	22		23
RTBr	no Δ	-4	-8	-15	-7	1	-3	-3		6
Kidneys										
AOW-% Δ from control	1	-4	-3	33	-1	2	1	22		48
RTB	1	2	16	173	18	3	13	59		90
RTBr	4	no Δ	no Δ	38	2	-1	3	27		57

Shaded areas indicate statistically significant difference from control group ( $p < 0.05$ ).

120-L: 120 mg/kg loratadine (active control group).

AOW: Absolute organ weight

RTB: Relative to body weight

RTBr: Relative to brain weight

*Gross Pathology:* The primary gross findings following the final sacrifice were likely due to the pharmacological effects of the drug and included dilatation in the gastrointestinal tract, the kidney, uterus and urinary bladder at a slightly higher incidence in drug-treated animals than in

controls (Table 9). Kidney discoloration and heart foci were also noted. In animals dying early, these findings, as well as stomach discoloration and reduced spleen and thymus size, were reported.

**Table 9.** Gross observations in rats following 3-month oral administration.

Observation	Males						Females					
	Final sacrifice		Dose (mg/kg)		n =		Final sacrifice		Dose (mg/kg)		n =	
	0	3	30	60	120	120-L	0	3	30	60	120	120-L
	10	10	10	10	1	10	10	10	8	4	0	4
Colon - dilatation	0	0	0	0	0	1	0	0	0	0	0	0
Heart - focus	0	0	0	0	0	1	0	0	0	0	0	0
Lg Intest. - dilatation	0	0	0	0	1	0	0	0	0	0	0	0
Kidney - discoloration	0	0	0	0	1	1	0	0	0	1	0	1
- dilatation	1	0	0	2	0	1	0	0	0	0	0	1
Testis - small	1	0	0	1	0	4						
Urinary bladder - dilatation	0	0	0	0	0	1	0	0	0	0	0	0
Uterus - dilatation							0	2	1	0	0	0
-small							0	0	0	1	0	1
Unscheduled deaths												
n =	0	0	0	0	9	0	0	0	2	6	10	6
Cecum - dilatation	0	0	0	0	1	0	0	0	0	1	0	3
Colon - dilatation	0	0	0	0	0	0	0	0	0	1	1	4
- dilated/impacted	0	0	0	0	0	0	0	0	0	0	1	0
Duodenum - dilatation	0	0	0	0	0	0	0	0	0	1	0	0
Ileum - dilatation	0	0	0	0	1	0	0	0	0	1	0	0
Lg Intest. - dilatation	0	0	0	0	1	0	0	0	0	0	2	0
- impaction	0	0	0	0	0	0	0	0	0	0	3	0
- stricture	0	0	0	0	0	0	0	0	0	0	1	0
Jejunum - dilatation	0	0	0	0	1	0	0	0	0	1	0	0
Kidney - discoloration	0	0	0	0	1	0	0	0	0	0	0	0
- dilatation	0	0	0	0	0	0	0	0	0	0	0	1
Liver - discoloration	0	0	0	0	0	0	0	0	0	0	1	0
- focus	0	0	0	0	0	0	0	0	0	0	0	1
Spleen - focus	0	0	0	0	1	0	0	0	0	0	0	0
-small	0	0	0	0	3	0	0	0	0	0	5	1
Stomach - dilatation	0	0	0	0	0	0	0	0	0	1	1	0
-discoloration	0	0	0	0	1	0	0	0	0	0	0	0
-enlarged	0	0	0	0	1	0	0	0	0	0	0	0
Thymus - small	0	0	0	0	0	0	0	0	0	0	1	0
Uterus - dilatation	0	0	0	0	0	0	0	0	1	0	0	0

**Histopathology:** Histological findings are summarized in Table 10. The primary findings were ubiquitous indicators of systemic phospholipidosis and included vacuolation, atrophy, necrosis, fibrosis and inflammatory cell infiltration. Findings were generally of greatest incidence and severity at the high SCH 34117 dose, while findings at the dose of 60 mg/kg was comparable to those at 120 mg/kg loratadine.

Table 10. Histological changes in rats following 3-month administration.

Histopathology	Males						Females						
	0	3	30	60	120	120-L	0	3	30	60	120	120-L	
<b>Adrenals – vacuolation</b>	<b>10</b>	<b>0</b>	<b>0</b>	<b>10</b>	<b>10</b>	<b>10</b>	<b>10</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>10</b>	<b>10</b>	<b>10</b>
Minimal	0			0	7	0	0			2	1	4	
Mild	0			0	0	0	0			0	9	2	
<b>Brain – vacuolation of choroid plexus</b>	<b>10</b>	<b>0</b>	<b>0</b>	<b>10</b>	<b>10</b>	<b>10</b>	<b>10</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>10</b>	<b>10</b>	<b>10</b>
Minimal	0			0	2	0	0			2	2	5	
Mild	0			0	8	0	0			6	5	1	
Moderate	0			0	0	0	0			1	3	3	
<b>Bone – cell infiltr, mononuc cell, myofiber</b>	<b>10</b>	<b>0</b>	<b>10</b>	<b>10</b>	<b>10</b>	<b>10</b>	<b>10</b>	<b>0</b>	<b>10</b>	<b>10</b>	<b>10</b>	<b>10</b>	<b>10</b>
Minimal -	0		0	0	5	0	0	0	6	1	5		
Mild	0		0	0	5	0	0	0	1	7	4		
Moderate	0		0	0	0	0	0	0	0	2	0		
<b>Vacuolation – myofiber</b>													
Minimal	0		0	0	6	0	0	0	7	0	6		
Mild	0		0	0	3	0	0	0	2	10	3		
Moderate	0		0	0	1	0	0	0	0	0	0		
<b>Fibrosis, myofiber</b>													
Minimal	0		0	0	6	0	0	0	2	2	5		
Mild	0		0	0	0	0	0	0	2	7	4		
<b>Degeneration, myofiber</b>													
Minimal	0		0	0	9	0	0	0	5	6	8		
Mild	0		0	0	0	0	0	0	2	0	0		
Moderate	0		0	0	0	0	0	0	1	0	0		
<b>Bone marrow –</b>	<b>10</b>	<b>0</b>	<b>10</b>	<b>10</b>	<b>10</b>	<b>10</b>	<b>10</b>	<b>0</b>	<b>10</b>	<b>10</b>	<b>10</b>	<b>10</b>	<b>10</b>
Hypercellularity – min	0		0	0	0	2	0	0	2	0	0		
Hypocellularity – min	0		0	0	1	0	0	0	0	4	2		
- mild	0		0	0	2	0	0	0	0	0	1		
Mastocytosis – min	0		0	0	1	0	0	0	0	0	0		
- mild	0		0	0	1	0	0	0	0	0	0		
<b>Vacuolation – scattere</b>													
minimal	0		0	0	5	0	0	0	2	2	5		
mild	0		0	0	3	0	0	0	1	5	1		
moderate	0		0	0	1	0	0	0	0	3	1		
<b>Atrophy, fat</b>													
Mild	0		0	0	1	0	0	0	0	0	0		
Moderate	0		0	0	6	0	0	0	0	8	3		
<b>Epididymides</b>	<b>10</b>	<b>10</b>	<b>10</b>	<b>10</b>	<b>10</b>	<b>10</b>							
<b>Cellular debris, lumina</b>													
Minimal	1	0	2	3	7	0							
Mild	0	0	3	6	2	8							
Moderate	0	0	0	0	0	1							
<b>Vacuolation, epithel</b>													
Minimal	1	0	6	1	0	2							
Mild	0	0	0	4	2	4							
Moderate	0	0	0	5	8	4							

Histopathology	Males						Females					
	0	3	30	60	120	120-L	0	3	30	60	120	120-L
Dose group (mg/kg)	0	3	30	60	120	120-L	0	3	30	60	120	120-L
Oligospermia												
Minimal	0	0	0	0	2	0						
Mild	0	0	1	0	1	2						
Moderate	1	0	0	1	0	2						
Severe	0	0	0	0	0	1						
Eyes - vacuolation of	10	0	10	10	10	10	10	10	10	10	10	10
Ciliary body, m-phage												
Minimal	0		0	0	6	0	0	0	0	1	8	0
Vacuolation, myofiber												
Minimal	0		0	6	5	5	0		1	10	7	10
Mild	0		0	0	5	0	0		0	0	3	0
Vacuolation, retinal, epithelium												
minimal	0		0	0	5	0	0	0	0	5	5	3
Gliosis - minimal	0		0	0	1	0	0	0	0	0	0	0
Heart	10	0	10	10	10	10	10	10	10	10	10	10
Cell. Infiltration mononuclear ce												
Minimal	0		0	0	5	2	0	0	0	1	4	7
Mild	0		0	0	1	0	0	0	0	1	3	2
Vacuolation, myofiber, base												
Minimal	0		0	1	6	4	2	2	6	6	3	3
Mild	0		0	0	0	0	0	0	0	2	0	6
Vacuolation, myfiber, Interstitial												
Minimal	0		0	0	8	0	0	0	0	3	2	1
Mild	0		0	0	0	0	0	0	0	0	8	5
Degeneration, myofibe minimal	1		0	0	3	0	1	1	1	0	0	0
Kidneys	10	0	10	10	10	10	10	10	10	10	10	10
Vacuolation, epithel												
Minimal	0		0	9	1	7	0	0	3	3	3	0
Mild	0		0	1	4	2	0	0	0	4	5	5
Moderate	0		0	0	5	0	0	0	0	3	2	5
Necrosis												
Minimal	2		0	6	9	5	0	0	1	6	6	7
Hyperplasia, epith, pel												
Mild	0		0	0	0	1	0	0	0	0	0	0
Erosion, pelvis												
Moderate	0		0	0	0	1	0	0	0	0	0	0
Dilatation, tubular												
Minimal	1		0	0	2	1	0	0	0	1	2	0
Mild	0		0	0	0	0	0	0	0	1	0	2
Moderate	0		0	0	1	0	0	0	0	0	0	0

Histopathology	Males						Females					
	0	3	30	60	120	120-L	0	3	30	60	120	120-L
Dose group (mg/kg)	0	3	30	60	120	120-L	0	3	30	60	120	120-L
Lymph nodes	10	10	10	10	10	10	10	1	10	10	10	10
Vacuolation, mophage												
Minimal	0	0	1	5	0	2	0	0	0	3	0	1
Mild	0	0	0	0	4	0	0	0	0	7	3	6
Moderate	0	0	0	0	6	0	0	0	0	0	7	3
Atrophy, lymphoid												
Minimal	0	0	0	0	3	0	0	0	0	2	2	3
Mild	0	0	0	0	0	0	0	0	0	1	5	2
Moderate	0	0	0	0	6	0	0	0	0	0	3	2
Liver	10	10	10	10	10	10	10	10	10	10	10	10
Cell. Infiltr., mononuc. cell, decreased	0	0	0	1	10	2	0	0	0	4	8	7
Vacuolation, kupfer ce												
Minimal	0	0	0	0	4	0	0	0	0	1	4	8
Mild	0	0	0	0	5	0	0	0	0	0	5	1
Moderate	0	0	0	0	1	0	0	0	0	0	0	0
Vacuolation, centrilob. hepatocellular												
Minimal	0	0	0	5	1	1	0	0	0	8	1	4
Mild	0	0	0	1	7	1	0	0	0	1	9	6
Moderate	0	0	0	0	2	0	0	0	0	0	0	0
Vacuolation, biliary, epithelium												
Minimal	0	0	0	6	0	4	0	0	2	1	0	0
Mild	0	0	0	1	1	2	0	0	1	2	0	2
Moderate	0	0	0	0	6	0	0	0	0	4	1	5
Severe	0	0	0	0	3	0	0	0	0	3	9	3
Hypertrophy, centrilob												
Minimal	0	0	0	0	1	0	0	0	5	5	1	2
Mild	0	0	4	2	8	0	0	0	3	2	9	4
Moderate	0	0	6	8	0	10	0	0	0	1	0	4
Lungs	10	0	10	10	10	10	10	10	10	10	10	10
Vacuolation, epithel												
Minimal	0		0	7	6	3	0	0	4	4	2	6
Mild	0		0	0	2	1	0	0	0	3	8	4
Vacuolation, al mac												
Minimal	0		0	1	1	4	0	0	5	0	8	3
Mild	0		0	9	8	4	0	0	2	6	2	5
Moderate	0		0	0	1	0	0	0	0	4	0	2
Material, proteinacious alveolar												
Minimal	0		0	3	6	0	0	0	0	4	9	1
Mild	0		0	0	3	0	0	0	0	1	1	0
Moderate	0		0	0	1	0	0	0	0	3	0	9

Histopathology	Males						Females					
	0	3	30	60	120	120-L	0	3	30	60	120	120-L
Dose group (mg/kg)	10	0	10	10	10	10	10	10	10	10	10	10
Esophagus												
Cell infiltr, mononuc cell												
minimal	0		0	0	6	1	0	0	0	5	5	6
mild	0		0	0	0	0	0	0	0	0	0	1
Vacuolation, myofiber												
minimal	0		0	3	2	1	0	0	1	3	1	0
mild	0		0	0	5	0	0	0	0	6	9	10
Degeneration, myofiber												
minimal	0		0	1	2	0	0	0	1	1	1	2
Ovaries							10	10	10	10	10	10
Vacuolation, sex cord												
Minimal							0	0	0	9	10	10
Mild							0	0	0	1	0	0
Vacuolation, corp lute												
Minimal							0	0	0	1	2	0
Mild							0	0	0	4	7	4
Moderate							0	0	0	4	1	5
Severe							0	0	0	0	0	1
Vacuolation, rete ducts												
Minimal							0	0	0	2	0	0
Mild							0	0	1	0	1	1
Moderate							0	0	0	0	2	1
Severe							0	0	0	0	1	0
Necrosis, granulosa cell												
Minimal							0	0	0	0	6	3
Mild							0	0	0	0	1	1
Atrophy, follicular												
Minimal							0	0	0	0	1	1
Pancreas	10	10	10	10	10	10	10	10	10	10	10	10
Single cell necrosis												
Minimal	0	0	0	0	1	0	0	0	0	0	0	0
Vacuolation, ductular												
Minimal	0	0	0	6	0	0	0	0	1	1	0	0
Mild	0	0	0	0	2	0	0	0	0	3	1	6
Moderate	0	0	0	0	6	0	0	0	0	0	4	2
Severe	0	0	0	0	2	0	0	0	0	1	5	1
Vacuolation, acinar cell												
Minimal	1	1	2	0	0	2	0	0	0	1	4	2
Mild	0	0	0	0	8	0	0	0	0	2	3	3
Moderate	0	0	0	0	0	0	0	0	0	0	2	0
Parathyroid glands												
Vacuolation, chief cell												
Minimal	0			0	9	0	0	0	0	4	7	8
Mild	0			0	0	0	0	0	0	2	0	1

Histopathology	Males						Females					
Dose group (mg/kg)	0	3	30	60	120	120-L	0	3	30	60	120	120-L
Pituitary gland	10	0	10	10	10	10	10	0	10	10	10	10
Vacuolation, pa anterior												
Minimal	0		0	1	9	2	0		0	10	10	10
Prostate	10	0	10	10	10	10						
Vacuolation, epithel												
Minimal	0		0	1	2	0						
Mild	0		0	0	6	1						
Moderate	0		0	0	1	0						
Immaturity												
Minimal	0		0	0	7	0						
Salivary gland	10	0	0	10	10	10	10	0	10	10	10	10
Vacuolation, sublingual, ductular												
Minimal	0			0	1	0	0		0	1	0	0
Mild	0			0	1	0	0		0	0	3	0
Moderate	0			0	7	0	0		0	8	7	10
Severe	0			0	1	0	0		0	0	0	0
Vacuolation, sublingual acinar cell												
Minimal	0			0	5	0	0		0	8	7	8
Mild	0			0	4	0	0		0	0	3	2
Vacuolation, parotid, ductular												
Minimal	0			0	5	0	0		0	4	6	5
Mild	0			0	3	0	0		0	2	4	5
Moderate	0			0	2	0	0		0	1	0	0
Vacuolation, parotid, acinar cell												
Minimal	9			7	0	3	6		8	4	0	1
Mild	0			0	4	0	0		0	2	6	7
Moderate	0			0	5	0	0		0	0	4	0
Vacuolation, submandib, ductular												
Minimal	0			0	2	0	0		0	4	0	2
Mild	0			0	4	0	0		0	5	6	5
Moderate	0			0	3	0	0		0	0	4	3
Severe	0			0	1	0	0		0	0	0	0
Vacuolation, submandib, acinar cell												
Minimal	0			0	3	0	0		0	5	3	1
Mild	0			0	0	0	0		0	0	1	0
Moderate	0			0	0	0	0		0	0	3	0
Necrosis, parotid												
Minimal	0			0	2	0	0		1	1	0	0
Necrosis, submandib												
Minimal	0			0	2	0	0		0	0	2	0

Histopathology	Males						Females					
	0	3	30	60	120	120-L	0	3	30	60	120	120-L
Atrophy, sublingual												
Minimal	0		0	8	0		0	0	5	4	8	
Mild	0		0	0	0		0	0	0	6	2	
Atrophy, parotid												
Minimal	0		0	3	0		0	0	0	1	2	
Mild	0		0	3	0		0	0	0	3	0	
Moderate	0		0	2	0		0	0	1	2	1	
Severe	0		0	2	0		0	0	0	4	2	
Atrophy, submandib												
Minimal	0		0	4	0		0	0	7	2	2	
Mild	0		0	2	0		0	0	1	3	2	
Moderate	0		0	0	0		0	0	0	2	1	
Seminal vesicles	10	0	10	10	10	10						
Vacuolation, epithel												
Minimal	1		0	6	0	3						
Mild	0		0	1	0	2						
Moderate	0		0	0	7	0						
Severe	0		0	0	3	0						
Immaturity												
Minimal	0		0	0	2	0						
Skeletal muscle	10	0	10	10	10	10	10	10	10	10	10	10
Cell. Infiltr., mononuc cell,												
Minimal	0		0	0	5	0	0	0	0	5	2	3
Mild	0		0	0	4	0	0	0	0	0	6	0
Moderate	0		0	0	0	0	0	0	0	0	2	1
Vacuolation												
Minimal	0		0	1	5	0	0	0	0	3	1	3
Mild	0		0	0	5	0	0	0	0	2	8	2
Moderate	0		0	0	0	0	0	0	0	0	1	0
Fibrosis, interstitial												
Mild	0		0	0	0	0	0	0	0	0	4	1
Degeneration, myofibe												
Minimal	0		0	0	4	0	0	1	1	3	6	1
Mild	0		0	0	3	0	0	0	0	0	2	1
Severe	0		0	0	0	0	0	0	0	0	0	1
Skin	10	0	10	10	10	10	10	0	10	10	10	10
Cell. Infiltr., mononuc cell,												
myofiber	0		0	0	3	0	0		0	1	7	4
Minimal												
Vacuolation, epith	0		0	1	2	0	0		0	4	1	2
Minimal	0		0	0	5	0	0		0	4	4	4
Mild	0		0	0	3	0	0		0	0	5	0
Moderate												
Vacuolation, myofiber	0		0	2	2	0	0		0	5	0	1
Minimal	0		0	0	3	0	0		0	4	4	4
Mild	0		0	0	5	0	0		0	0	6	4
Moderate												

Histopathology	Males						Females					
	0	3	30	60	120	120-L	0	3	30	60	120	120-L
Necrosis, epithelial												
Minimal	0		0	0	1	0	0		0	1	1	0
Mild	0		0	0	1	0	0		0	0	0	0
Atrophy, fat												
Minimal	0		0	0	2	0	0		0	0	0	2
Mild	0		0	0	1	0	0		0	0	0	0
Moderate	0		0	0	1	0	0		0	0	4	2
Severe	0		0	0	6	0	0		0	0	6	3
Harderian glands	10	0	0	10	10	10	10	10	10	10	10	10
Single cell necrosis												
Minimal	0			0	0	0	0	0	0	3	5	3
Mild	0			0	0	0	0	0	0	0	1	2
Vacuolation, epithel												
Minimal	0			0	4	0	0	0	0	1	4	2
Mild	0			0	0	0	0	0	0	0	0	1
Pigment accum, lumin												
Minimal	0			0	6	0	0	0	0	0	1	2
Atrophy												
Minimal	1			0	5	0	0	0	1	3	5	7
Mild	0			0	0	0	0	0	0	0	1	0
Stomach	10	0	0	10	10	10	10	0	10	10	10	10
Vacuolation, epith												
Minimal	0			0	4	0	0		0	0	2	0
Vacuolation, myofiber												
Minimal	0			0	2	0	0		0	2	1	2
Mild	0			0	7	0	0		0	4	9	5
Necrosis, mucosal												
Minimal	0			0	1	0	0		0	0	0	0
Congestion, mucosal												
Minimal	0			0	1	0	0		0	0	0	0
Large intestine	10	0	0	10	10	10	10	0	10	10	10	10
Vacuolation, lymphoid nodule, macrophage												
Minimal	0			0	1	0	0		0	0	1	0
Mild	0			0	1	0	0		0	0	0	0
Vacuolation, myofiber												
Minimal	0			0	8	0	0		0	0	3	0
Mild	0			0	0	0	0		0	2	5	2
Dilatation, luminal												
Minimal	0			0	0	0	0		0	0	0	0
Mild	0			0	1	0	0		0	0	0	0
Severe	0			0	0	0	0		0	0	1	3

Histopathology	Males						Females					
	0	3	30	60	120	120-L	0	3	30	60	120	120-L
Small intestine	10	0	0	10	10	10	10	0	10	10	10	10
Vacuolation, lymphoid nodule, macrophage	0			0	3	0	0	0	1	0	0	
Minimal												
Vacuolation, duodenal gland	0			0	7	0	0	0	5	7	5	
Minimal												
Vacuolation, lamina propria, macrophage	0			0	6	0	0	0	2	5	3	
Minimal	0			0	6	0	0	0	0	5	0	
Mild	0			0	3	0	0	0	3	6	4	
Vacuolation, myofiber	0			0	0	0	0	0	1	1	0	
Minimal												
Mild												
Spleen	10	0	10	10	10	10	10	1	10	10	10	10
Vacuolation, m-phage												
Minimal	0		0	0	0	1	0	0	0	1	0	0
Mild	0		0	0	2	0	0	0	0	9	0	6
Moderate	0		0	0	3	0	0	0	0	0	3	4
Severe	0		0	0	5	0	0	0	0	0	7	0
Fibrosis, capsular												
Minimal	0		0	0	1	0	0	0	0	0	0	0
Atrophy, lymphoid												
Minimal	0		0	0	1	0	0	0	0	3	1	4
Mild	0		0	0	2	0	0	0	0	1	1	2
Moderate	0		0	0	2	0	0	0	0	0	6	0
Sever	0		0	0	5	0	0	0	0	0	2	3
Testes	10	10	10	10	10	10						
Cellular debris, luminal												
Minimal	1	0	1	6	1	3						
Mild	0	0	0	1	0	6						
Vacuolation, sertoli cell												
Minimal	7	6	5	5	1	3						
Mild	0	0	0	1	0	2						
Moderate	1	0	0	0	0	5						
Hypospermatogenesis												
Minimal	1	4	2	3	1	1						
Mild	0	0	0	0	0	1						
Moderate	1	0	0	1	0	2						
Severe	0	0	0	1	0	3						
Thyroid	10	0	0	10	10	10	10	0	10	10	10	10
Vacuolation												
Minimal	0			0	3	0	0	0	4	7	6	
Mild	0			0	4	0	0	0	3	0	0	
Moderate	0			0	3	0	0	0	0	1	3	

Histopathology	Males						Females					
	0	3	30	60	120	120-L	0	3	30	60	120	120-L
Thymus	10	10	10	10	10	10	10	10	10	10	10	10
Cell infiltr, neutrophil												
Minimal	0	0	0	0	1	0	0	0	0	0	0	0
Vacuolation, m-phage												
Minimal	0	0	2	3	2	0	0	0	2	7	0	2
Mild	0	0	0	0	8	0	0	0	0	2	2	5
Moderate	0	0	0	0	0	0	0	0	0	0	8	1
Necrosis, scattered lymphoid												
Minimal	0	0	0	0	2	0	0	0	1	1	2	0
Mild	0	0	0	0	1	0	0	0	0	0	2	0
Moderate	0	0	0	0	0	0	0	0	0	0	1	0
Hemorrhage												
Minimal	0	0	0	0	1	0	0	0	0	0	0	0
Mild	0	0	0	0	1	0	0	0	0	0	1	0
Moderate	0	0	0	0	0	0	0	0	0	0	0	1
Atrophy, lymphoid												
Minimal	0	0	0	0	1	0	0	0	0	1	1	0
Moderate	0	0	0	0	1	0	0	0	0	1	4	3
Severe	0	0	0	0	5	0	0	0	0	0	5	1
Tongue	10	0	0	10	10	10	10	0	10	10	10	10
Cell infiltr., mononuc cell,												
Minimal	0			0	8	0	0	0	1	5	2	
Mild	0			0	1	0	0	0	0	3	0	
Moderate	0			0	0	0	0	0	0	1	0	
Vacuolation												
Minimal	0			0	9	0	0	0	7	1	8	
Mild	0			0	1	0	0	0	2	9	1	
Fibrosis, interstitial												
Minimal	0			0	0	0	0	0	0	3	0	
Trachea	10	0	10	10	10	10	10	10	10	10	10	10
Vacuolation, m-phage												
Minimal	0		0	0	1	0	0	0	0	2	3	
Mild	0		0	0	0	0	0	0	0	2	6	0
Moderate	0		0	0	0	0	0	0	0	0	0	1
Vacuolation, epithel												
Minimal	0		0	3	1	5	0	0	3	0	0	0
Mild	0		0	5	5	0	0	0	0	3	7	9
Moderate	0		0	0	4	0	0	0	0	4	3	1
Necrosis, epithelial												
Severe	0		0	0	0	0	0	0	0	1	1	0
Uterus							10	10	10	10	10	10
Immaturity												
Minimal							0	0	0	2	1	0
Mild							0	0	0	1	2	0
Moderate							0	0	0	1	3	8
Severe							0	0	0	0	3	0

Histopathology	Males						Females					
	0	3	30	60	120	120-L	0	3	30	60	120	120-L
Vacuolation, myometr												
Minimal							0	0	0	4	5	1
Mild							0	0	0	1	5	5
Vacuolation, endometrium, m-phag												
Minimal							0	0	2	4	1	2
Mild							0	0	0	5	8	6
Moderate							0	0	0	0	1	1
Vacuolation, epithel												
Minimal							0	0	2	5	0	1
Mild							0	0	0	3	1	3
Moderate							0	0	0	2	9	6
Urinary bladder	10	0	0	10	10	10	10	10	10	10	10	10
Vacuolation, epithel												
Minimal	0			0	3	2	0	0	0	2	1	2
Mild	0			0	5	0	0	0	0	2	6	3
Moderate	0			0	2	0	0	0	0	1	2	3
Vacuolation, myofiber												
Minimal	0			0	6	0	0	0	2	4	5	4
Mild	0			0	4	0	0	0	0	0	4	1
Vagina							10	0	10	10	10	10
Cell infiltr, mononuc												
cell, myofiber							0		0	1	2	4
Minimal												
Vacuolation, m-phage							0		0	3	0	0
Minimal							0		0	1	7	6
Mild							0		0	0	3	2
Moderate												
Vacuolation, myofiber							0		0	3	3	5
Minimal							0		0	2	5	5
Mild												
Vacuolation, urethral							0		0	0	1	0
Minimal												
Vacuolation, epithel							0		0	1	6	3
Minimal							0		0	1	3	5
Mild												
Mammary glands	10	0	0	10	10	10	10	0	10	10	10	10
Vacuolation												
Minimal	0			0	0	0	0		0	5	1	4
Mild	0			0	0	0	0		0	4	9	5
Atrophy												
Minimal	0			0	2	0	0		0	0	0	0
Mild	0			0	2	0	0		0	0	0	0
moderate	0			0	2	0	0		0	0	0	0

120-L: 120 mg/kg loratadine active control group.

*Toxicokinetics:* Plasma concentrations increased supra-proportionally in a dose-dependent manner and were gender-dependent with exposure greater by up to 3.3-fold in females than in

males following administration of SCH 34117 and loratadine (Table 11). SCH 34117 was slowly absorbed. The SCH 34117 exposure resulting from loratadine administration was similar to that observed at 60 mg/kg SCH 34117. Drug accumulation was observed with multiple dose administration, especially at the lowest dose. Loratadine exposure following loratadine administration was approximately 7 to 10-fold less than corresponding SCH 34117 exposure indicating extensive metabolism of loratadine.

**Table 11.** Toxicokinetics of SCH 34117 and loratadine.

Parameter		Dose (mg SCH 34117/kg)								Dose (mg SCH 29851/kg)	
		3		30		60		120		120	
		Day 1	Wk 9	Day 1	Wk 9	Day 1	Wk 9	Day 1	Wk 9	Day 1	Wk 9
<b>SCH 34117</b>											
C <sub>max</sub> (ng/ml)	Males	23.7	252	611	1150	1590	1650	2010	*	1250	2990
	Females	77	200	1000	2140	2140	4770	2320	*	1950	3370
T <sub>max</sub> (hr)	Males	2.5	8	4	12	8	12	12	*	2.5	4
	Females	1	2.5	8	12	8	2.5	4	*	8	12
AUC (0-24 hr) (ng.hr/ml)	Males	169	1950	9490	26100	29000	34500	39000	*	23900	37800
	Females	556	1890	17700	42600	39800	69200	46300	*	39000	64200
R	Males		11.5		2.8		1.2		*		1.6
	Females		3.4		2.4		1.7		*		1.6
<b>SCH 29851</b>											
C <sub>max</sub> (ng/ml)	Males									858	560
	Females									1260	779
T <sub>max</sub> (hr)	Males									1	2.5
	Females									1	1
AUC (0-24 hr) (ng.hr/ml)	Males									4070	3940
	Females									5480	5990
R	Males										--
	Females										1.09

R = AUC (0-24 hr) week 9 / AUC (0-24 hr) day 1      NA: not applicable

\* not assessed due to high mortality

A NOAEL of 3 mg/kg and 30 mg/kg was identified in females and males, respectively, due to kidney necrosis and reduced body weight gain. Systemic phospholipidosis (primarily vacuolation, atrophy and necrosis) was the main toxicity and was noted in organ systems throughout the body. Toxicity was more prominent in SCH 34117-treated animals based on a mg/kg basis. However, the toxicity profile was similar between the loratadine-treated group and the 60 mg/kg SCH 34117 as indicated by the pharmacokinetic similarities between the two groups.

**Monkey, 3-Month Oral (Gavage) Toxicity**

Study # [redacted] Schering Study #: 98212 Report #: P-6976 Volume: 23.4

**Study Dates:** Starting date: 7/1/1998; report issued: 6/1999  
**Testing Lab:**  
**Test Article:** SCH 34117 (Batch 97-34117-X-03-RA; purity not provided); SCH 29851 (Batch MI-A-00851; purity not provided)  
**Concentration:** 1.2 to 14.4 mg/ml  
**Dose Volume:** 5 ml/kg  
**GLP:** This report was submitted with a signed GLP statement.  
**QA report:** Yes.

**Methods:** Cynomolgus monkeys were assigned to the following treatment groups:

Dose	0	6	12	18/24*	22/72*
(mg SCH 34117/kg/day):					
No./sex	4	4	4	4	4

\*: Groups dosed with 18 mg/kg SCH 34117 or 22 mg/kg loratadine were increased to 24 and 72 mg/kg, respectively, during Study week 6.

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Each monkey received a daily dose of vehicle, test drug or comparative dose of loratadine by oral (gavage) administration for 3 months. The following observations were made:

Clinical observation . . . daily  
Body weight . . . . . weekly  
Food consumption . . . daily  
Water consumption . . . not assessed  
twice pre-study, Days 28 and 79; included body temperature, heart rate, and respiration rate  
Ophthalmoscopy . . . . Pre-test and week 12  
ECG . . . . . Days -2, -5, 28 and 79; assessment included body temperature, heart rate, respiration, systolic blood pressure, diastolic blood pressure  
Hematology . . . . . Days -12 and -5, and Days 23 and 92  
Clinical chemistry . . . . Weeks -2, and Days 12 and 24  
Urinalysis . . . . . Days -12/13 and -5/6, and Days 22/23 and 91/92  
Enzyme induction . . . . Liver samples assayed for protein content, cytochrome P450 content, and 7-ethoxyresorufin O-deethylase. Results to be reported separately by sponsor.  
Organ weights . . . . . at sacrifice (for specific tissues/organs see Addendum, page 32)  
Gross pathology . . . . . at sacrifice  
Histopathology . . . . . at sacrifice; organs/tissues collected from the control (vehicle and active), high-dose monkeys, monkeys sacrificed moribund and all gross lesions (for specific tissues/organs see Addendum, page 32).