Study Site: [redacted]
Study Date: 1/28/1982 - 3/5/1982
GLP/QAC Compliance: Yes
Basis of Dose Selection: Results from a preliminary study by dosing rabbits with 5, 10, 20, 30, 40, 60, 80, and 100 mg/kg of UH-AC 62 XX for 10 days showed gastric ulcers in one animal at 80 mg/kg. Therefore, 80 mg/kg was set as the high-dose.
Study Design: Groups of pregnant rabbits as shown in the following table were orally given 0, 5, 20, and 80 mg/kg/day of UH-AC 62 XX from Gestation Days 6→18.

Group	Compound	Dose (mg/kg)	Dosing Period	Nº of Rabbits
0	Vehicle Control	0	GD 6→18	18
1	UH-AC 62 XX	5		18
2		20		18
3		80		18

The following observations were conducted.

- Clinical Signs and Mortality - 1x/day.
- Body Weights - 1x/day on Gestation Days 1, 7-16, 21 and 28.
- Food and H_2O Consumption - Not monitored.
- Necropsy - Gestation Day 29. All organs were macroscopically examined.
- Female Reproductive and Litter Parameters -
  - Nº of copra lutea;
  - Nº of implantation;
  - early (discernible placental remnants) and late resorption (discernible fetal remains);
  - fetal weights;
  - fetal external abnormalities; and
  - fetal skeletal (x-ray) and visceral [redacted] abnormalities.

Results:

- Clinical Signs and Mortality - There were 7 deaths (1 @ 0 and 6 @ 80 mg/kg) due to either dosing errors (1 each @ 0 and 80 mg/kg) or drug-related GI injury. One control female with a malformation of the upper incisors had delivered prematurely on Gestation Day 29. Data from these animals were not included in the final analysis. Occasionally, signs of little or no feces were seen in one or two animals from each group.
- Body Weights - High dose group had body weight losses during GD 6→9 and lower body weight gains as compared to the controls. Mean body weight changes in each group during Gestation period are shown in the following table.

Dose (mg/kg)	Mean Body Weight Gain (g) Normalized to Gestation Day 1					
	GD 7	GD 8	GD 13	GD 18	GD 21	GD 28
Control	32.5	42.4	58.9	116.8	172.6	339.2
5	41.6	28.1	81.1	161.1	169.1	288.6
20	27.8	24.5	72.1	131.7	144.5	271.3
80	-8.7 (↓126.8%)	-26.2 (↓161.8%)	16.7 (↓71.6%)	54.3 (↓53.5%)	87.9 (↓49.1%)	231.9 (↓31.8%)

GD = Gestation Day; ↓ = Decrease.

- Food and H_2O Consumption - Not monitored.
- Necropsy - No treatment-related gross pathological lesions were identified in all surviving animals. Characteristics of treatment-caused GI toxicity (hemorrhages in the gastric or intestinal mucosa and/or ulcers in the stomach or intestine) were observed in all high-dose rabbits that died during the study.

- Female Reproductive and Litter Parameters - Dose-dependent increases in the Nº of viable fetuses, preimplantation loss and resorption rates were identified in UH-AC 62 XX treated groups. The incidences of mean litter and reproductive parameters are presented in the following table.

Mean Parameter		Control	5 mg/kg	20 mg/kg	80 mg/kg
Nº of Litters Evaluated		13	9	10	7
Corpora Lutea		8.7	8.8	8.7	8.6
Implantations		7.9	7.8	7.5	6.6
Viable Fetuses		7.5	6.4	6.0	5.3*
Sex (%)	♂	53.7	45.3	46.5*	53.9
	♀	46.3	54.7	48.5	46.1
Total Nº of Resorptions		0.4	1.3	1.4	1.3
Fetal Weight (g)		39.0	40.8	39.7	39.6
Preimplantation Loss (%)		8.3	12.3	15.4	28.5
Resorption Rate (%)		5.7	16.7	21.7	17.8

+ due to fetus Nº 203/53 whose sex could not be determined

No treatment related increases in the incidence of malformation and variation were observed. The incidence of major findings for variations and malformations in each group is listed as follows.

Findings	Nº of Findings in the Fetuses: Absolute/Relative Values (%)				
	Control	5 mg/kg	20 mg/kg	80 mg/kg	Historical Control (%)*
Nº Litters Evaluated	13	9	10	7	566
Petechial Hemorrhages in the Ovaries	2 (2.0)	3 (5.2)	-	2 (5.4)	2.0
Nº of Fetuses Evaluated	98	66	60	37	3694
Runts/runts	2 (2.0)	1 (1.7)	2+ (3.3)	-	1.1
VARIATIONS					
Flexure of limbs	3 (3.1)	-	3 (5.0)	2 (5.4)	0.7
Retinal folds	7 (7.1)	7 (12.1)	-	-	30.8
Hypoplasia of gallbladder	2 (2.0)	1 (1.7)	1 (1.7)	-	0.1
Hypoplasia of 12th pair of ribs				2 (5.4)	0.1
Dilatation of the auricles of the heart	1 (1.0)		-		
MALFORMATIONS					
Cor triloculare uni venthiculi + Truncus arteriosus persistens with common trunk of carouds and subclavian arteries of both sides	1 (1.0)				1.1

* These data origin from an internal historical data set which is filed in the Teratology Laboratory at Boehringer Ingelheim
+ One dead runt no. 214/4 (body weight: 20 g) was excluded from calculation

Therefore, NOEAL for maternal toxicity was 20 mg/kg, embryo/fetal toxicity was <5 mg/kg; and UH-AC 62 XX was not teratogenic at oral doses up to 80 mg/kg in rabbits.

2.4.2.4. U82-0509 Teratogenicity study with the substance UH-AC 62 XX in rabbits Segment II (Supplementary study). 17 May 1983. (Vol. 2.047, p 1)

Study Nº: 41 I
Report Nº: U82-0509
Study Aims: To determine the embryotoxicity and teratogenic effects of UH-AC 62 XX when administered to pregnant rabbits on Gestation Days 6→18.
Compound:
Dose and Route:
Vehicle Control:
Animal: Himalayan rabbits, strain (SPF), ~6 months of age, weighing ~2300 g. 24/group.
Study Site: Boehringer Ingelheim Pharma KG
Study Date: 11/8/1982 - 12/15/1982
GLP/QAC Compliance: Yes

Study Design: Groups of pregnant rabbits as shown in the following table were orally given 0, 1, 20, and 60 mg/kg/day of UH-AC 62 XX from Gestation Days 6→18.

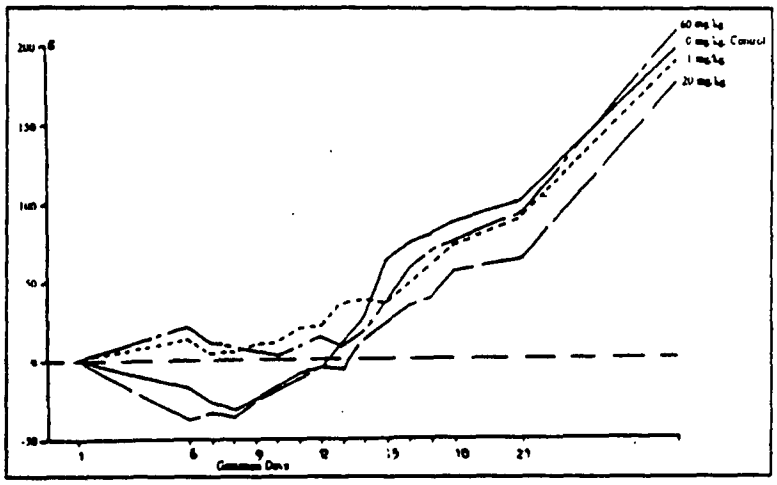
Group	Compound	Dose (mg/kg)	Dosing Period	Nº of Rabbits
0	Vehicle Control	0	GD 6→18	18
1	UH-AC 62 XX	1		18
2		20		18
3		60		18

The following observations were conducted.

- Clinical Signs and Mortality - 1x/day.
- Body Weights - 1x/day on GD 1, 6-18, 21 and 28.
- Food and H_2O Consumption - Not monitored.
- Necropsy - GD 29. All organs were macroscopically examined.
- Female Reproductive Parameters -
  - Nº of copra lutea;
  - Nº of implantation;
  - Nº of live and dead fetuses;
  - Nº of resorption (early and late); and
  - pre-implantation loss [(Nº of copra lutea - Nº of implantation)/Nº of copra lutea x 100].
- Fetal Paramenters -
  - external abnormalities;
  - fetal weight; and
  - fetal skeletal (x-ray) and visceral [redacted] abnomalies.

Results:

- Clinical Signs and Mortality - A total of 5 high-dose dams died during the study with pathological findings of hemorrhages in gastric or intestinal mucosa and/or ulcers in the GI. Clinical signs of slight anemia and lethagy were noted in 4/5 animals. One of these animals had convulsions prior to death. One high-dose dam was found to have injured hind limb on Gestation Day 6. One control died as the result of dosing error. Occasionally, signs of little or no feces were seen in some animals from each group.
- Body Weights - Reduced body weights were noted in dams @ 0 and 20 mg/kg during GD 1→12 as shown in the right figure. However, comparable mean body weights were obtained for all groups.



- Food and H_2O Consumption - Not monitored.
- Necropsy - Treatment-related GI toxicity (ulcers) was observed in 5 high-dose dams that died during study. No test article-caused pathological changes were identified in any of surviving dams.
- Female Reproductive and Litter Parameters - A Dose-dependent increase in resorption rate was observed. Dams (1 @ 20 and 4 @ 60 mg/kg) with total resorptions were excluded from litter parameter analysis. Significantly decreased mean fetal weights (↓ 8%) were identified in Group 2

(1 mg/kg). The following table lists mean incidence of reproductive and fetal parameters for each group.

Parameter		Control	1 mg/kg	20 mg/kg	60 mg/kg
Nº of Mated Females		18	18	18	18
Nº of ♀ with Total Resorption		0	0	1	5
Nº of litters evaluated		16	15	17	11
Corpora lutea		7.69	8.60	8.24	8.36
Implantations		6.94	7.07	7.24	7.18
Viable fetuses		6.25	6.07	5.71	3.91
Sex Ratio(%)	♂	48.9	58.3	44.6	56.7
	♀	51.1	41.7	55.4	43.3
Total number of resorptions		0.69	0.93	1.53	3.27*
Fetal weight (g)		39.96	36.77*	38.13	39.00
Nº of Runts[1]		0	6	1	1
Preimplantation loss (%)		9.22	17.37	12.40	14.89
Resorption rate (%)		10.52	13.84	22.13	46.99*

[1] Runt - Fetuses weighed <65% of normal fetal weight (<25.8 g); * p<5%.

The following table described malformations observed in the present study.

Dose (mg/kg)	Nº of Litter Evaluated	Nº of Fetus Evaluated	% Incidence (fetus/litter)	Dam Nº	Fetus Nº	Sex	Malformations
0	16	100	0/0	-	-	-	-
1	15	92	3.3/20.0	110	3	?	open eyes; fetus was dead
				113	3	M	fused sternebrae; bend sternum
				115	6	M	fused sternebrae
20	16	97	1.0/6.3	205	4	M	absence of gallbladder
60	7	43	4.7/28.6	304	6	W/F	cleft lip and cleft palate; unilateral anophthalmia; facial bones shortened and laterally disarranged; septal defect of the heart
				307	4	W/F	septal defect of the heart with considerable dilatation of the aortic arch

Therefore, NOEAL for maternal toxicity was 20 mg/kg, embryo/fetal toxicity was 1 mg/kg. It appeared that UH-AC 62 XX cause teratogenic effect at an oral dose up to 60 mg/kg as 2/43 fetuses had septal defect of heart at this dose. **Although data from a previous study (2.4.2.3 U82-0078) showed no malformations in fetuses from dams @ 80 mg/kg, it is difficult to obtain the consistency between these two studies as low number of litters and fetuses were evaluated. However, the incidence of cardiovascular defect in the rabbit is rare (historical control: 0.01% provided by the sponsor); therefore, the relationship of observed malformation to treatment with UH-AC 62 XX in the present study cannot be excluded.**

2.4.2.5. U83-0068 Study of the substance UH-AC 62 XX for embryolethal effects in rabbits Segment-II Supplementary study. 14 October 1983. (Vol. 2.048, p 1)

Study Nº: 99 I
Report Nº: U83-0068
Study Aims: To determine the embryotoxicity effect of UH-AC 62 XX when administered to pregnant rabbits on Gestation Days 6→18.
Compound: [redacted]
Dose and Route: [redacted]
Vehicle Control: [redacted]
Animal: Himalayan rabbits, strain [redacted] (SPF), ~6 months of age, weighing ~2200 g. 24/group.
Study Site: Boehringer Ingelheim Pharma KG [redacted]
Study Date: 9/8/1983 (?) (Mating started) - 12/9/1983 (?) (Necropsy concluded)

GLP/QAC Compliance: Yes

Study Design: Groups of pregnant rabbits as shown in the following table were orally given 0, 1, 3, 8, and 20 mg/kg/day of UH-AC 62 XX from Gestation Days 6→18.

Group	Compound	Dose (mg/kg)	Dose Vol.	Dosing Period	Nº of Rabbits
0	Vehicle Control	0	5 ml/kg	Gestation Days 6→18	24
1	UH-AC 62 XX	1			24
2		3			24
3		8			24
4		20			24

The following observations were conducted.

- Clinical Signs and Mortality - 1x/day.
- Body Weights - GD 1, 6-18, 21 and 25.
- Food and H_2O Consumption - Not monitored.
- PK/TK - GD 17/18, 4/group.
- Necropsy - GD 17/18 (4/group, PK study) and 25. All organs were macroscopically examined.
- Female Reproductive Parameters -
  - Nº of copra lutea;
  - Nº of implantation;
  - Nº of live and dead fetuses;
  - Nº of resorption (early and late); and
  - pre-implantation loss [(Nº of copra lutea - Nº of implantation)/Nº of copra lutea x 100].
- Fetal Examinations - Not performed.

Results:

- Clinical Signs and Mortality - One dam @ 1 mg/kg became difficult to be inserted with gastric tube from GD 9→13 and had signs of accelerated respiration and wheezing. Another 1 mg/kg dam (Nº 124) had broken right hind leg on GD 10 and was sacrificed on GD 17 due to deteriorated health condition. This animal was found to have complete resorption during necropsy.
- Body Weights - Comparable mean body weight was noted for UH-AC 62 XX treated and control groups. However, reduced cummulative weight gains during the treatment, GD 6→18, were noted in animals @ 1 and 8 mg/kg. Weight loss was noted in the Nº 124 rabbit @ 1 mg/kg that had broken leg on GD 10. The following table shows cummulative weight gains for each group during gestation period.

Dose	Cumulative Weight Gains (g) Normalized to GD 1								Cumulative Weight Gains (g)	
(mg/kg)	GD 6	GD 7	GD 8	GD 10	GD 13	GD 18	GD 21	GD 25	GD 6-18	GD 6-25
Control	64.5	70.6	81.7	105.0	109.7	165.3	207.0	288.7	100.8	224.2
1	63.1	73.7	76.8	86.8	113.0	155.3	154.8	260.3 (↓10%)	91.5 (↓9.2%)	197.7 (↓12%)
3	69.1	67.4	65.6 (↓20%)	68.4 (35%)	98.0 (↓11%)	177.7	179.4 (↓14%)	296.5	108.6	227.4
8	52.7 (↓18%)	48.9 (↓31%)	41.6* (↓49%)	52.2* (↓50%)	85.0 (↓23%)	134.8 (↓18%)	133.3 (↓36%)	232.6 (↓19%)	82.1 (↓19%)	179.9 (↓20%)
20	18.7* (↓71%)	29.4* (↓58%)	22.8* (↓72%)	45.5* (↓51%)	63.6* (↓42%)	120.1 (↓27%)	121.9 (↓41%)	226.4 (↓22%)	101.4	207.7 (↓7%)

* p≤0.05.

- Food and H_2O Consumption - Not monitored.
- PK/TK - **No data were presented.**
- Necropsy - No treatment-related gross lesions were identified. Findings of black-brown discoloration in the cortico-medullary junction of the kidneys (9 @ 0, 7 @ 1 mg/kg, 16 @ 3 mg/kg, 18 @ 8 mg/kg and 12 @ 20 mg/kg), renal calculi in the left kidney and cysts on the

surface of both kidneys (1 @ 1 mg/kg), renal calculi in the right kidney (1 @1 mg/kg) and pale liver with with a sandy colour (1 @ 3 mg/kg) were identified.

- Female Reproductive Parameters - A slight increase in the Nº of total resorptions was observed in the high-dose group.

Parameter (means)		Control	1 mg/kg	3 mg/kg	8 mg/kg	20 mg/kg
Nº of ♀ Mated		24	24	24	24	24
Nº of Not Pregnant		6	2	4	1	5
Nº with Total Resorption		0	1	0	0	0
Nº of Litters Evaluated		18	22/21[a]	20	23	19
Corpora Lutea		8.56	8.23/8.24[a]	8.90	8.09	8.79
Implantations		6.89	7.32/7.29[a]	8.30[a]	7.17	7.58
Viable Fetuses		6.61	6.41/6.71[a]	7.65	6.48	6.58
Resorptions	Early	0.22	0.82/0.48[a]	0.45	0.48	0.84
	Late	0.06	0.1/0.1[a]	0.2	0.13	0.16
	Total	0.28	0.91/0.57[a]	0.65	0.61	1.00[a,b]
Preimplantation Loss (%)		19.92	10.55[a]/11.05[a,b]	6.92[a]	11.69	13.32
Resorption Rate (%)		4.51	12.28/8.10[a]	8.54	8.60	12.51

[a] The dam (Nº 124) that had broken leg and complete resorption was excluded from analysis.
[b] The difference to the control became significant if the dam (Nº 124) that had broken leg with complete resorption was excluded from calculation.

Therefore, the NOAEL for maternal toxicity was 20 mg/kg and embryo/fetal toxicity was 8 mg/kg.

Note: In the original and subsequent two amendment submissions, sections of data were illegible and report was poorly translated and not comprehensible. After repeated requests, the 4th amendment dated September 3, 1999 was received on September 7, 1999. The report indicated that treatment started on September 15, 1983 and terminal sacrifice started on September 12, 1983. Again, it reflects the faulty preparation of study report and the negligence of QAC unit.

2.4.3. PERINATAL/POSTNATAL (SEGMENT III) STUDY

2.4.3.1. U92-0308 Reproduction Studies with meloxicam (UH-AC 62 XX) in Rats Dosed Orally during Perinatal and Postnatal Period (Segment III). (Vol. 2.048, p 169)

Study Nº: 359-3321
Report Nº: U92-0308
Study Aims: To determine the effects of UH-AC 62 XX on gestation, parturition, and lactation in the dams and the development, survival, behavior and reproductive performance of the pups.
Compound:
Dose and Route:
Vehicle Control:
Animal: Sprague-Dawley (Slc:SD) rats, ~11 weeks of age, weighing 187.6-228.3 g, 24/group.
Study Site:
Study Date: 10/2/1990 - 10/8/1991
GLP/QAC Compliance: Yes (Japanese)
Study Design: Pregnant female rats were randomly assigned to 4 different groups and given various oral doses of UH-AC 62 XX as shown in the following table.

Group	Compound	Dose (mg/kg/day)	Dosing Volume (ml/kg)	Dosing Duration	Nº of Animals/Group
0	0.5% MC	0	10	GD 17→LD 21	24♀
1	UH-AC 62 XX	0.125			
2		0.25			
3		0.5			

The following observations were conducted.

- Clinical Signs and Mortality - 2x/day.
- Body Weights and Food/H_2O Consumption - GD 0, 4, 7, 17→21; LD 0, 4, 7, 14, and 22.
- Necropsy - On LD 22, all F_0 dams were sacrificed. The liver, spleen, kidneys, adrenals, heart, lungs, thymus, ovaries, uterus, and GI tracts were thoroughly examined. The Nº of implantation traces were recorded to calculate birth index [(Nº of live births/Nº of implantation sites) x 100].
- Delivery and Neonatal Examination - All dams were allowed to deliver naturally and to nurse newborns for 21 days. The gestation period and live birth rate were recorded. The following parameters were recorded for the newborns:
  - litter size, sex;
  - Nº of stillbirths and livebirths;
  - external malformations;
  - body weights - PND 0, 4, 7, 14, and 22; and
  - mortality - 1x/day up to PND 70.
- Differentiation Examination of Newborns - On PND 4, 4/sex newborns from each litter were randomly selected and remaining newborns were sacrificed. Four-day survival rate was calculated. The following parameters were examined for the development and differentiation of the newborns.
  - unfolding of the ear;
  - hair growth;
  - eruption of incisors;
  - seperation of eyelids;
  - decent of the testes; and
  - vaginal opening.
- F_1 Behavior and Functional Tests - The following tests were carried out in 1/sex from each litter.
  - voluntary exercise with rotating wheel - Day 21, to determine the total number of wheel rotation in 30 min.
  - pain, Preyer (an auditory test), righting, free fall and vision reflex - Day 20;
  - open-field for mood behavior - Week 4;
  - rotarod treadmill - Week 5; and
  - nultiple water T-maze test for learning ability - Week 6.
- F_1 Reproductivity Test - At Week 11, 1/sex from each litter was allowed to mate for 14 days. Males were sacrificed at the end of mating period. Reproductive orgnas from any confirmed not fertile ♂ and not pregnant ♀ were preserved in [redacted] and examined microscopically. The confirmed copulated females were housed individually. The following observations were carried out:
  - body weights - GD 0, 4, 8, 12, 16, and 21;
  - C-section - GD 21, all F_1 females. The following reproductive parameters were also determined: Nº of copra lutea; Nº of implantation; Nº of live and dead fetuses; Nº of resorption (early and late). Viable fetuses were sexed, weighed, and examined for external abnormalities. Aproximately $^1/_3$ F_2 fetuses were fixed in [redacted] and the other $^2/_3$ were preseved in 95% alcohol.

Results:

Effects on the F_0 Dams:

- Mortality & Clinical Signs - A total of 5 deaths occurred during the treatment. Signs of pilorection, anemia, and dark feces were noted in 7 @ 0.125, 16 @ 0.25 and 22 @ 0.5 mg/kg. One dam @ 0.5 mg/kg had vaginal bleeding on GD 23.
- Body Weights & Food Consumption - Slightly lower mean body weight (↓5-6%) was noted in 0.5 mg/kg dams during LD 0→7.
- Reproductive Performance - Dose-depedent significant changes in the ♀ reproductive performace parameters, such as prolonged gestation period and the length of delivering time, reduced birth index, increased Nº of stillbirths and reduced Nº of live births were observed.

Parameters		Dose (mg/kg)			
		0	0.125	0.25	0.5
Nº Pregnant ♀		24	24	24	24
Nº of ♀ Deliver Live Offspring		24	23	23	17
Nº of Dead ♀		0	1	0	4
Delivery Index*		100	100	95.8	85
Length of Gestation (Days)		21.4	21.9**	22.4**	22.7**
Birth Index		92.4	81.8	71.9*	44.9**
Nº of Implantation		13.4	13.7	13.0	13.9
Nº of Stillbirths		3.0	23.0*	63.0**	116.0**
Nº of Live Birth		12.4	11.2	9.0**	6.3**
Sex Ratio (♂/♀)		154/143	142/115	99/118	62/63
Newborn Body Weight (g)	♂	5.8	6.0	6.1* (↑5.2%)	5.9
	♀	5.4	5.6	5.8** (↑7.4%)	5.6

* Delivery Index = (Nº of ♀ with Live Births/Nº of Implantations)x100; * p<5%; ** p<1%.

- Necropsy Findings - Gastric ulcers were found in $^{1}/_{4}$ ♀ @ 0.5 mg/kg that died during gestation period and in $^{3}/_{6}$ @ 0.25 mg/kg and $^{7}/_{12}$ @ 0.5 mg/kg that had no livebirth or lost all pups during lactation. In addition, lesions with characteristics of ulcer or pit in the stomach were identified in 1 each dam @ 0.25 and 0.5 mg/kg/day at PND 21 terminal sacrifice. Other observed gross pathological alterations included discoloration in the liver, spleen, and kidney, atrophy of spleen, edema in the lungs or thymus, and swelling of adrenals and kidney.

Effects on the F_1:

- Mortality - A dose-dependent increase in mortality was noted in the pups during PND 0→4. The 4-day survivals and weaning rate of F_1 offspring are presented as follows:

Dose (mg/kg)	Nº of Dams	Nº of Live F_1				Survival Rate on PND 4		Weaning Rate (PND 22)	
		PND 0		PND 4					
		♂	♀	♂	♀	♂	♀	♂	♀
0	24	154	143	152	139	98.6	97.0	95.8	94.8
0.125	23	142	115	119	99	80.0	76.8	96.3	99.1
0.25	23	99	118	84	102	73.7	75.4	98.8	94.7
0.5	17	62	63	45	42	48.3**	50.0*	97.9	100.0

- Body Weights - F_1 born to F_0 dams @ 0.25 mg/kg had significantly higher mean body weight on PND 0 (♂: ↑5.2%; ♀: ↑7.4%). No significant differences in mean body weights mesured on PND 4→77 were noted.
- Visceral and External Findings in F_1 - Mean incidence of visceral, skeletal and external findings at various stages are presented in the following table

Parameters	Control	0.125 mg/kg	0.25 mg/kg	0.5 mg/kg
EXTERNAL FINDING AT BIRTH				
Nº of Offspring Examined (at birth)	291	257	217	125
Nº of Offspring with Anomaly at birth	0	0	0	0
Nº of Offspring with Anomaly after Birth (%)	1 (0.3)	3 (1.2)	3 (1.4)	0
Unilateral Anophthalmia	0	0	1	0
Abnormal Eyeball (Cataract)	0	1	2	0
Crooked tail	1	2	0	0
SKELETAL FINDINGS - PND 22				
Nº of Offspring Examined	91	69	61	28
Nº of Offspring with Anomaly	0	0	0	0
No. of offspring with Variation (5)	22 (24.2)	17 (24.6)	20 (32.8)	5 (17.9)
Cervical Rib	9 (9.9)	5 (7.2)	9 (14.8)	1 (3.6)
Shortening of the 13th Rib	0	0	0	1 (3.6)
Hypoplasia or Non-Ossification of Cervical Vertebral Body (%)	6 (6.6)	0	4 (6.6)	0
Bipartite Vertebral Body (%)	8 (8.8)	6	6 (9.8)	
Dumbbell Shaped Vertebral Body	0	2	0	0
Splitting of The 1st Lumbar Transverse Process	1 (1.1)	4 (5.8)	6* (9.8)	2 (7.1)
VISCERAL FINDINGS - PND 22				
Nº of Offspring Examined	91	69	61	28
Nº of Offspring with Anomaly	4 (4.4)	1 (1.4)	1 (1.6)	4 (14.3)
Hepatodiaphragmatic Nodule	4	1	1	3 (10.7)
Accessory Spleen	0	0	0	1
VISCERAL FINDINGS - PND 56				
Nºof Offspring Examined	46	37	33	15
Nº of Offspring with Anomaly	3 (6.5)	6 (16.2)	5 (15.2)	0
Hepatodiaphragmatic Nodule	0	1	1	0
Accessory Spleen	0	0	1	0
Cyst Formation In Kidney	0	1	0	0
Enlarged Testis	2	0	0	0
Atrophy of Testis	0	0	1	0
Dilatation of Uterus	1	3	2	0
Fat Necrosis	0	1	0	0
VISCERAL FINDINGS - THE END OF FERTILITY TEST				
Nº of Offspring Examined	46	38	35	16
Nº of Offspring with Anomaly (%)	11 (23.9)	3 (7.9)	2 (5.7)	3 (18.0)
Hepatodiaphragmatic nodule	3 (6.5)	0	0	0
Dark Green Zone in Liver	0	0	0	1
Dark Red Focus in Liver	1	0	0	0
Accessory Spleen	1	1	0	0
Thickened Capsule of Spleen	3	0	0	0
Pitting Surface in Kidney	0	0	1	0
Dilatation of Renal Pelvis	1	0	0	0
Enlarged Testis	2	0	0	1
Atrophy of Testis	1	1	0	0
Dilatation of Uterus	0	1	0	0
Ovarian Bursa Distended with Fluid	1	0	0	0
Fat Necrosis	0	0	1	1

- Physical Development Reflex and Behavior in F_1 - Examination of physical development showed that F_1 of all UH-AC 62 XX treated groups had ealier separaton of auricle (3.2, 2.7, 2.4, and 2.6 days for 0, 0.125, 0.25, and 0.5 mg/kg, respectively) and eyelid (15.7, 14.8, 14.4, and 14.7 days for 0, 0.125, 0.25, and 0.5 mg/kg, respectively) and F_1 of dams @ 0.125 mg/kg had early eruption of incisors (10.9 vs 11.6 days) and delayed descent of testes (23.4 vs 21.8 days). In addition, ♂ of 0.5 mg/kg group had higher a higher Nº of falls (8.5 vs 3.0 in control) in the rota-rod treadmill test.
- Reproductive Functions in F_1 - A lower Nº of implantations was noted in F_1 dams at 0.5 mg/kg. Mean values of fertility indices and reproductive performance parameters for each group are listed in the following table. No external abnormalities were identified in F_2 fetuses.

Parameters		Dose (mg/kg)			
		0	0.125	0.25	0.5
Nº of F_1 Dams Mated		23	17	17	8
Nº of Copulated at 1st Mating		23	17	17	7
Nº of ♀ Pregnant		23	16	16	7
Copulated/Mated (%)		100	94.5	100	87.5
Pregnant/Copulated (%)		100	94.1	94.1	100
Nº of Corpora Lutea		14.3	14.5	14.9	13.6
Nº of Implantations		13.7	13.6	13.9	12.3*
Resorbed Rate (%)	Early	9.4	6.7	11.4	13.4
	Late	0	0.4	0.6	0
	Total	9.4	7.1	12.0	13.4
Nº of Live Fetuses	♂	6.0	6.2	6.2	5.6
	♀	6.4	6.4	6.1	5.0
Sex Ratio (♂/♀)		49/51	49/51	50/50	51/49
Body Weight (g)	♂	4.98	5.02	5.04	5.14
	♀	4.71	4.79	4.71	4.88
External Malformation of F_2		0	0	0	0

Therefore, NOAEL for maternal toxicity was 0.125 mg/kg; reproductive toxicity of F_0 and F_1 was <0.125 and 0.25 mg/kg, respectively; developmental toxicity was <0.125 mg/kg. UH-AC 62 XX was not teratogenic at oral doses up to 0.5 mg/kg.

2.5. GENOTOXICITY STUDIES

2.5.1. *IN VITRO STUDIES*

2.5.1.1. U80-0054 Mutagenicity studies with the substance UH-AC 62 XX in the [redacted] 10 December 1980 (Vol. 2.049, p 13)

Report Nº: U80-0054
Study Aim: To evaluate mutagenic potential of UH-AC 62 XX using [redacted]
Compound: [redacted]
Dose: [redacted]
Vehicle Control: [redacted]
Indicator Cells: [redacted]
S9 Mix: [redacted]
Positive Control: [redacted]
Test Article Exposure Time: 72 hr at 37°C
Study Location: [redacted]
Study Date: 6/24/1980 - 9/16/1980
Compliance with GLP/QAU: Not Indicated

Results: Precipitation occurred at concentrations ≥2500 μg/plate. **The positive control, benzoapyrene was not mutagenic under the condition without metabolic activation for all tester strains and for TA1535 in the presence of activation mixture. Therefore, it is difficult to draw any conclusions.**

2.5.1.2. U88-0540 Mutagenicity study with UH-AC 62 XX in the [redacted] 25 July 1988. (Vol. 2.049, p 31)

Study Nº: GEN TOX 05/88

Report Nº: U88-0540
Study Aim: To evaluate mutagenic potential of UH-AC 62 XX using
Compound:
Dose:
Vehicle Control:
Indicator Cells:
S9 Mix:
Positive Control:

Test Article Exposure Time: 48 hr at 37°C
Study Location:
Study Date: 5/3/1988 - 7/8/1988
Compliance with GLP/QAU: Yes (OECD)

Results: Precipitation occurred at the concentration of 2500 μg/plate. No increased incidence of revertants of all tester strains with or without metabolic activation was observed. Therefore, UH-AC 62 XX, up to 2500 μg/plate, was not mutagenic under current experimental condition.

2.5.1.3. U84-0633 Mutagenicity study with substance UH-AC 62 XX in the V79 (HGPRT) test. 20 July 1984. (Vol. 2.049, p 56)

Report Nº: U84-0633
Study Aim: To evaluate mutagenic potential of SC-58635 using
Compound:
Dose:
Negative Control:
Positive Controls:
Indicator Cells:
S9 Mix:
Exposure Time: 2hr at 37°C
Study Location:
Study Date: 4/4/1984 - 5/31/1984
Compliance with GLP/QAU: Yes
Study Design: Cells were treated with various concentrations of UH-AC 62 XX or positive control compounds for 2 hr with or without metabolic activation.

Results: No increased incidence of mutant cells under current testing condition was observed. **However, it is difficult to make a conclusion stating that UH-AC 62 XX was not mutagenic as cells were only exposed briefly to meloxicam (2 hr). The exposure to test articles is usually**

3-6 hr in the standard procedures for *in vitro* cytogenetic evaluation of chromosomal damage in mammalian cells other than mouse lymphoma

2.5.1.4. U89-0094 Mutagenicity study with UH-AC 62 XX: Chromosomal aberrations in human lymphocytes in-vitro. 11 January1989. (Vol. 2.049, p 89)

Report Nº: U89-0094
Study Nº: GEN TOX 04/88
Study Aims: To assess the potential of UH-AC 62 XX to induce chromosomal aberrations in human lymphocytes
Compound:
Dose:
Vehicle Control:
Indicator Cells:
S9 Mix:
Positive Control:
Exposure Time:
Study Location:
Study Date: 2/22/1988 - 3/24/1988
Compliance with GLP/QAU: Yes

Results: Data showed that UH-AC 62 XX did not cause a increased chromosomal aberrations in human primary lymphocyte at doses up to 50 μg/ml under the condition without S9 and 100 μg/ml under the condition with S9.

2.5.2. *IN VIVO STUDIES*

2.5.2.1. U83-0069 Mutagenicity study with substance UH-AC 62 XX in the micronucleus test in mice. 01 December 1983. (Vol. 2.049, p 118)

Report Nº: U83-0069
Study Aims: To assess the potential of UH-AC 62 XX to induce micronuclei in the mouse bone marrow polychromatic erythrocytes
Compound:
Dose and Route:
Vehicle Control:
Positive Control:
Animals: ♂ and ♀ (SPF) mice, 10-week old, weighing ~35 g.
Sampling Time: 24 hr post-Ⓐ for all dose and 48 and 72 hr post-Ⓐ for UH-AC 62 XX and CP treated groups
Study Location:
Study Date: 11/7/1983- 11/10/1983
Compliance with GLP/QAU: Yes
Study Designs: Animals were randomly assigned to 3 dose groups (vehicle control; UH-AC 62 XX:300 mg/kg; cyclophosphamide: 30 mg/kg). All mice were monitored for signs of toxicity, moribundity, and mortality Animals (2-5/sex) were sacrifice at 24, 48 or 72 post single dose treatment and bone marrow smears were prepared. A total of 1000 polychromatic erythrocytes (PE) per animal were evaluated for micronucleated cells (MNE).

[1] ICH S2B: Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals, 16 July, 1997.

Results: Two ♂ in UH-AC 62 XX group were found dead 60 hr post dose and necropsy was not performed. The survival mice in this group had clinical signs of ruffled fur and lethargy. The ratios of PE/NE (normochromatic erythrocyte) and MNE/1000 PE for each group are shown in the following table. A slight increased mean % MNE/1000 PE was noted for UH-AC 62 XX treated males at 24 hr post dose.

Groups	Dose (mg/kg)	N	Sampling Time (hr)											
			24				48				72			
			♂		♀		♂		♀		♂		♀	
			PE/NE	%MNE	PE/NE	%MNE	PE/NE	%MNE	PE/NE	%MNE	PE/NE	%MNE	PE/NE	%MNE
Vehicle Control	0	5/sex	0.85	0.1	0.50	0.14								
UH-AC 62 XX	300	5/sex	0.53	0.28	0.52	0.08	0.78	0.18	0.92	0.08	0.89	0.13	1.02	0.1
Cyclophosphamide	30	2/sex	0.44	1.45	0.70	1.90	0.14	1.35	0.27	0.30	0.23	0.45	0.48	0.25

2.5.2.2. U92-0301 UH-AC 62 XX: Mutagenicity study in the mouse bone marrow [redacted] after oral treatment. 15 May 1992. (Vol. 2.049, p 136)

Report Nº: U92-0301
Study Nº: GEM TOX 14/91
Study Aims: To assess the potential of UH-AC 62 XX to induce micronuclei in the mouse bone marrow polychromatic erythrocytes
Compound: [redacted]
Dose and Route:
Vehicle Control:
Positive Control:
Animals: ♂ and ♀ [redacted] (SPF) mice, 6-8 weeks old, weighing 15-29 g. 5/sex/group/time point.
Sampling Time: 24 hr post-Ⓡ for all dose and 48 hr post-Ⓡ for the high-dose group
Study Location: [redacted]
Study Date: 7/9/1991 - 7/11/1991
Compliance with GLP/QAU: Yes
Study Designs: Animals were randomly assigned to 5 dose groups (vehicle control: UH-AC 62 XX: 375, 150 and 300 mg/kg; cyclophosphamide: 30 mg/kg). All mice were monitored for signs of toxicity, moribundity, and mortality. Animals (2-5/sex) were sacrifice at 24 or 48 post single dose treatment and bone marrow smears were prepared. A total of 1000 polychromatic erythrocytes (PE) per animal were evaluated for micronucleated cells (MNE).

Results: There were no treatment-related clinical signs observed. Treatment with UH-AC 62 XX at doses up to 300 mg/kg did cause an increase in the ratio of MNE and had no effects on PE/ME ratio. Therefore, UH-AC 62 XX was not clastogenic in the present study.

2.5.2.3. U84-0220 Mutagenicity study with the substance UH-AC 62 XX in [redacted] in mice. 27 February 1984. (Vol. 2.049, p 160)

Report Nº: U84-0220
Study Aims: To assess the potential of UH-AC 62 XX to induce DNA mutation in *S. typhimurium* using [redacted] in the mouse.
Compound: [redacted]
Dose and Route:
Vehicle Control:
Positive Control:

Compound	*S. typhimurium*	Dose (mg/kg)
2-Amino-fluorene (2-AF)	TA 97	400
Diethylnitrosamine (DENA)	TA 98	100
Cyclophosphamide (CP)	TA 100	200

Animals: ♂ and ♀ [redacted] (SPF) mice, 6-8 weeks old, 4/sex for vehicle control and UH-AC 62 XX treatment groups, 2/sex for (+) groups
Indicator Cells: [redacted]
Liver Sampling Time: [redacted]
Study Location: [redacted]
Study Date: 1/10/1984 - 2/2/1984
Compliance with GLP/QAU: Yes
Study Designs: Animals were orally given vehicle control, UH-AC 62 XX: (200 and 400 mg/kg for TA97 and TA 100 tester strain; 150 and 300 mg/kg for TA 98 tester strain) or positive controls followed by iv injection of 0.25 ml ($1.45\text{-}3.99 \times 10^{10}$/ml) of *S. typhimurium*, TA 97, TA 98 or TA 100. All mice were monitored for signs of toxicity, moribundity, and mortality. Animals were sacrifice 2 hr post-R and the bacteria were recovered from the liver homogenates. The bacterial colonies were determined 48 hr after incubation at 37°C.

Results: Treatment with UH-AC 62 XX did not cause increased mutations in TA97, 98, and 100. **It is difficult to draw any conclusions from presented equivocal information as the positive controls, cyclophosphamide (200 and 500 mg/kg) and 2-AF (400 mg/kg) did not cause increases in the number of TA 100 and TA 97 revertants, respectively.**

2.6. SPECIAL TOXICOLOGY STUDIES

2.6.1. IMMUNOGENICITY OF UH-AC 62 XX

2.6.1.1. U90-0358 Intracutaneous sensitization study with UH-AC 62 XX in the guinea pig. (Vol. 2.038, p 62)

Study Nº: I 01-89
Report Nº: U90-0358
Study Aims: To determine the sensitizing properties of UH-AC 62 XX in guinea pigs following intracutaneous administration and topical dermal application.
Compound: [redacted]
Vehicle Control: [redacted]
Positive Control: [redacted]
Dose and Route: [redacted]
Animals: 34♂ and 34 ♀ guinea pigs [redacted] months of age, weighing ~300 g
Study Site: [redacted]
Study Date: 11/21/89 - 1/6/90
GLP/QAC Compliance: Yes
Study Design: The following table lists the detail treatment schedules for the control and test groups. All animals were weighed on Days 0, 22, and 38. Cutaneous reactions were evaluated at 24, 48, and 72 hr post each challenge.

Groups	Compound	Day	Treatment Schedule*	Site 1	Site 2	Site 3
A	UH-AC 62 XX (N=10/sex)	0	1st Sensitization	0.1 ml FCA	0.1 ml 2.5 mg in Vehicle	0.1 ml 2.5 mg in Vehicle/ FCA (1:2)
		8	2nd Sensitization	0.1 ml 2.5 mg UH-AC 62 XX in Vehicle		
		22	1st Challenge	0.1 ml 2.5 mg UH-AC 62 XX in Vehicle		
		38	2nd Challenge	0.1 ml 2.5 mg UH-AC 62 XX in Vehicle		
B	Vehicle Control (N=5/sex)	0	1st Sensitization	0.1 ml FCA	0.1 ml Vehicle	0.1 ml Vehicle/FCA (1:2)
		8	2nd Sensitization	0.1 ml Vehicle		
		22	1st Challenge	0.1 ml Vehicle		
		38	2nd Challenge	0.1 ml Vehicle		
C	(+) Control : DNBC (N=2/sex)	0	1st Sensitization	0.1 ml FCA	0.1 ml 0.3% DNCB	0.1 ml 0.3% DNCB/FCA (1:2)
		8	2nd Sensitization	0.1 ml 0.3% DNCB		
		22	1st Challenge	0.1 ml 0.3% DNCB		
		38	2nd Challenge	-		

* The 1st induction was done on 3 sites of left scapular region by intracutaneous (ic) injection. The 2nd induction was done on the right scapular region via ic administration; The 1st challenge was given by ic injection on the left side and epicutaneous injection on contralateral (right) side; the 2nd challenge was given by ic injection on the right side.

FCA = Freund's modified complete adjuvant

Results: No effect on body weight was noted. No skin reactions to the challenge applications of vehicle control. Pinhead-size reddening around puncture site was observed at 48-72 hours post challenge with UH-AC 62 XX. On contrast, DNCB, (+) control, caused bean-size thickening of skin at 24 hr post challenge, and it reached a hazelnut size with necrotic center by 48-72 hr post challenge.

2.6.1.2. U94-0091 Examination of UH-AC 62 XX eye drops 0.3% in a skin sensitization test in guinea pigs[redacted]

Study Nº: 8725/93

Report Nº: U94-0091

Study Aims: To determine the skin sensitizing properties of 0.3% UH-AC 62 XX ophthalmic solution in guinea pigs following intracutanous administration and topical dermal application.

Compound: [redacted]

Vehicle Control:

Positive Control:

Dose and Route: Detailed dosages and routes of application are shown in the following table.

Animals: [redacted] white guinea pigs, ~70 days of age, weighing 342-462 g, 20/group

Study Site: [redacted]

Study Date: 10/19/1993 -11/12/1993

GLP/QAC Compliance: Yes

Study Design: The following table lists the detail treatment schedules for the control and test groups. All animals were weighed on Days -1 and 23/24. Cutaneous reactions were evaluated at 24, 48, and 72 hr post challenge. The reactions were evaluated based on the 5-point scale for erythema and eschar formation (0 = no reaction; 1 = very slight erythema; 2 = well defined erythema; 3 = moderate to severe erythema; 4 = severe erythema to slight eschar formation) and edema formation [0 = no edema; 1 = very slight edema; 2 = slight edema (edge of area well defined by definite raising); 3 = moderate edema (raised ~1 mm); 4 = severe edema (raised >1 mm and extending beyond area of exposure)].

Day	Treatment Schedule	Skin Induction Site (in an area of 3 x 4 cm)		
		Site 1	Site 2	Site 3
VEHICLE CONTROL GROUP (20 ANIMALS)				
0	Intradermal Injection	0.1 ml FCA:0.9% NaCl (1:1)	0.1 ml vehicle control eye drops	0.1 ml vehicle control eye drops in FCA (1:1)
6	Topical Pre-treatment	0.5 ml 10% w/w sodium lauryl sulfate in vaseline		
7	Topical Induction	2 ml vehicle control eye drops (in an area of 5 x 6 cm) secured by an overwrap with tape for 48 hr.		
21	Challenge	2 ml 3% UH-AC 62 XX eye drops on the L flank and 2 ml vehicle control eye drops on the R flank secured with tape for 24 hr.		
UH-AC 62 XX (20 ANIMALS)				
0	Intradermal Injection	0.1 ml FCA:0.9% NaCl (1:1)	0.1 ml 3% UH-AC 62 XX eye drops	0.1 ml 3% UH-AC 62 XX eye drops FCA (1:1)
6	Topical Pre-treatment	0.1 ml 10% w/w sodium lauryl sulfate in vaseline		
7	Topical Induction	2 ml 3% UH-AC 62 XX eye drops secured by an overwrap with tape for 48 hr.		
21	Challenge	2 ml 3% UH-AC 62 XX eye drops on the L flank and 2 ml control cream on the R flank secured with tape for 24 hr.		
POSITIVE CONTROL (20 ANIMALS)				
0	Intradermal Injection	0.1 ml FCA:0.9% NaCl (1:1)	0.1 ml 1% $K_2Cr_2O_7$	0.1 ml 1% $K_2Cr_2O_7$ in FCA (1:1)
6	Topical Pre-treatment	0.5 ml 10% w/w sodium lauryl sulfate in vaseline		
7	Topical Induction	2 ml .0 % $K_2Cr_2O_7$ secured by an overwrap with tape for 48 hr		
21	Challenge	2 ml 0.1% $K_2Cr_2O_7$ on the L flank and 2 ml control cream on the R flank secured with tape for 48 hr.		

L = Left; R = Right.

Results: No effect on body weight was noted. One positive control animal died on Day 8. No skin reactions were recorded 24-72 hours post challenge with 1% UH-AC 62 XX CreSa, Parfenac® cream or vehicle control cream. On contrast, [redacted] caused very slight→moderate erythema 24-72 hours post challenge. **The study itself may not be valid for the below addressed problems; therefore, no conclusion can be drawn.**

Note: Based on the body weight data, it appeared that the positive control animals in the current study were also used in the following study (Study Nº: 8463/93). However, the sponsor did not indicate the repeated using of data from the same group of animals for two different study reports. In addition, one animal that died during the study had different initial body weights as shown in these two reports (Vol. 2.38, p 106 and 148) and reported dates for body weight measurement were different in these two studies. The sponsor needs to clarify the discrepancy between two study reports. Apparently, two studies were conducted at different times, 10/19/1993-11/12/1993 for Study Nº: 8725/93 (Report Nº: U94-0091) and 3/14/1994-4/18/1994 for Study Nº: 8463/93 (Report Nº: U94-0316). The sponsor needs to provide the actual time frame when the positive control group was conducted. The DSI should be notified to inspect laboratory reports.

2.6.1.3. U94-0316 Examination of UH-AC 62 XX Cresa 1% in a skin sensitization test in guinea pigs [redacted]

Study Nº: 8463/93
Report Nº: U94-0316
Study Aims: To determine the skin sensitizing properties of 1% UH-AC 62 XX cream in guinea pigs following intracutanous administration and topical application.
Compound: [redacted]
Vehicle Control:
Reference Compound:
Positive Control:
Dose and Route:
Animals: ♀[redacted] white guinea pigs, ~30 days of age, weighing 262-367 g, 20/group

Study Site: [redacted]

Study Date: 3/14/1994-4/18/1994

GLP/QAC Compliance: Yes

Study Design: The following table lists the detail treatment schedules for the control and test groups. All animals were weighed on Days -1 and 25/26. Cutaneous reactions were evaluated at 24, 48, and 72 hr post challenge. The reactions were evaluated based on the 5-point scale for erythema and eschar formation (0 = no reaction; 1 = very slight erythema; 2 = well defined erythema; 3 = moderate to severe erythema; 4 = severe erythema to slight eschar formation) and edema formation [0 = no edema; 1 = very slight edema; 2 = slight edema (edge of area well defined by definite raising); 3 = moderate edema (raised ~1 mm); 4 = severe edema (raised >1 mm and extending beyond area of exposure)].

Day	Treatment Schedule	Skin Induction Site (in an area of 3 x 4 cm)		
		Site 1	Site 2	Site 3
CONTROL GROUP (20 ANIMALS)				
0	Intradermal Injection	0.1 ml FCA:0.9% NaCl (1:1)	0.1 ml control cream	0.1 ml control cream in FCA (1:1)
6	Topical Pre-treatment	0.5 ml 10% w/w sodium lauryl sulfate in vaseline		
7	Topical Induction	2 ml control cream (in an area of 5 x 6 cm) secured by an overwrap with tape for 48 hr.		
21	Challenge	2 ml 1% UH-AC 62 XX cream on the L flank and 2 ml control cream on the R flank secured with tape for 24 hr.		
UH-AC 62 XX (20 ANIMALS)				
0	Intradermal Injection	0.1 ml FCA:0.9% NaCl (1:1)	0.1 ml 1% UH-AC 62 XX cream	0.1 ml 1% UH-AC 62 XX cream FCA (1:1)
6	Topical Pre-treatment	0.1 ml 10% w/w sodium lauryl sulfate in vaseline		
7	Topical Induction	2 ml 1% UH-AC 62 XX cream (in an area of 5 x 6 cm) secured by an overwrap with tape for 48 hr.		
21	Challenge	2 ml 1% UH-AC 62 XX cream on the L flank and 2 ml control cream on the R flank secured with tape for 24 hr.		
Parfenac® cream (20 ANIMALS)				
0	Intradermal Injection	0.1 ml FCA:0.9% NaCl (1:1)	0.1 ml Parfenac® cream	0.1 ml Parfenac® cream in FCA (1:1)
6	Topical Pre-treatment	0.5 ml 10% w/w sodium lauryl sulfate in vaseline		
7	Topical Induction	2 ml Parfenac® cream (in an area of 5 x 6 cm) secured by an overwrap with tape for 48 hr.		
21	Challenge	2 ml Parfenac® cream on the L flank and 2 ml control cream on the R flank secured with tape for 24 hr.		
POSITIVE CONTROL (20 ANIMALS)				
0	Intradermal Injection	0.1 ml FCA:0.9% NaCl (1:1)	0.1 ml 1% $K_2Cr_2O_7$	0.1 ml 1% $K_2Cr_2O_7$ in FCA (1:1)
6	Topical Pre-treatment	0.5 ml 10% w/w sodium lauryl sulfate in vaseline		
7	Topical Induction	2 ml 1.0% $K_2Cr_2O_7$ (in an area of 5 x 6 cm) secured by an overwrap with tape for 48 hr		
21	Challenge	2 ml 0.1% $K_2Cr_2O_7$ on the L flank and 2 ml control cream on the R flank secured with tape for 48 hr.		

L = Left, R = Right.

Results: No effect on body weight was noted. One positive control animal died 2 days post 2nd induction (topical). No skin reactions were recorded 24-72 hours post challenge with 1% UH-AC 62 XX CreSa, Parfenac® cream or vehicle control cream. On contrast, [redacted] caused very slight→moderate erythema 24-72 hours post challenge.

2.6.1.4. U90-0277 Cutaneous Sensitization with the Formulation UH-AC 62 XX 1% Gel, in guinea pigs. (Vol. 2.038, p 161)

Study Nº: I-TOX 04-90

Report Nº: U90-0277

Study Aims: To determine the skin sensitizing properties of 1.0% UH-AC 62 XX gel in guinea pigs following intracutanous administration.

Compound: [redacted]

Vehicle Control:

[redacted]

Positive Control: [redacted]
Dose and Route:
Animals:
Study Site:
Study Date: 3/12/1990 - 4/13/1990
GLP/QAC Compliance: Yes
Study Design: The following table lists the detail treatment schedules for the control and test groups. All animals were weighed on Days 0 and 22. Cutaneous reactions were evaluated at 24, 48, and 72 hr post challenge.

Groups	Compound	Day	Treatment Schedule*	Site 1	Site 2	Site 3
1	UH-AC 62 XX (N=10/sex)	0	Intradermal Injection	0.1 ml FCA	0.1 ml 1% UH-AC 62 XX Gel	0.1 ml 1% UH-AC 62 XX Gel / FCA (1:2)
		8	Topical Induction	1 g of 1% UH-AC 62 XX Gel		
		22	Topical Challenge	0.1 ml 1% UH-AC 62 XX Gel on the left side and 0.1 g Vehicle Gel on the right side		
2	Vehicle Control (N=5/sex)	0	Intradermal Injection	0.1 ml FCA	0.1 ml Vehicle Gel	0.1 ml Vehicle Gel/FCA (1:2)
		8	Topical Induction	0.1 g Vehicle Gel		
		22	Topical Challenge	0.1 ml 1% UH-AC 62 XX Gel on the left side and 0.1 g Vehicle Gel on the right side		
3	(+) Control : DNBC (N=2/sex)	0	Intradermal Injection	0.1 ml FCA	0.1 ml 0.3% DNCB	0.1 ml 0.3% DNCB/FCA (1:2)
		8	Topical Induction	0.1 ml 0.3% DNCB		
		22	Topical Challenge	0.1 ml 0.3% DNCB on the left side and 0.1 ml ETOH on the right side		

* The 1st induction was done on 3 sites of left scapular region by intracutaneous injection. The 2nd induction was done on the left scapular region via epicutaneous application for 48 hr; The challenge was given by epicutaneous application of UH-AC 62 XX on left side and vehicle control on the right side for 24 hr.

FCA = Freund's modified complete adjuvant

Results: No effect on body weight was noted. One each ♂ in Groups 2 and 3 died 24 hr post 2nd induction (topical) without any clinical symptoms. No skin irritation was recorded 24-72 hours post challenge with 1% UH-AC 62 XX gel or vehicle gel. On contrast, [redacted] caused reddening skin on the area of application at 24 hr post challenge; by 48-72 hr post challenge, an increase in the severity of reddening accompany with a thickening of the skin around application area was noted.

Note: Skin scores of individual animals were not submitted.

2.6.1.5. U92-0428 UH-AC 62 XX: Immunogenicity study after subcutaneous plantar administration in [redacted] mice [redacted]

Report N°: U92-0428
Study Aims: To determine the immunogenic potential of UH-AC 62 XX by using the [redacted]

Compound: [redacted]
Vehicle Control:

Positive Control: [redacted]
Dose and Route: [redacted]
Animals: ♀ mice, ~6 weeks of age
Study Site: [redacted]
Study Date: 9/22/1988 - 11/8/1988
GLP/QAC Compliance: Yes
Study Design: A total of 4 experiments were conducted. The dose and volumes of each test article are presented in the following table. Test compound, placebo, or (+) control chemical were injected into the right hind footpad, mice were sacrificed on Day 6, and popliteal lymph nodes from each side of the same dose group were pooled and store in ice-cold phosphate buffer. The surrounding fat and connective tissues were trimmed off, then the nodes were blot dried and weighed. The cells from each side pooled nodes were prepared for phenotypic staining with fluorochrome-labeled antibodies (CD 4 and CD8) and analyzed.

Group	Compound	N° of Mice
Experiment 1: (9/22/1998)		
1	Phenitoin, 1 mg (0.02 ml)	5♀
2	UH-AC 62 XX 1 mg (0.02 ml)	5♀
3	Placebo (0.02 ml)	5♀
Experiment 2: (10/21/1988)		
1	Phenitoin, 1 mg (0.02 ml)	5♀
2	UH-AC 62 XX 1 mg (0.02 ml)	5♀
3	Placebo (0.02 ml)	5♀
Experiment 3: (10/26/1988)		
1	Phenitoin, 1 mg (0.02 ml)	5♀
2	UH-AC 62 XX 1 mg (0.02 ml)	5♀
3	Placebo (0.02 ml)	5♀
4	Untreated control	5♀
Experiment 4: (11/8/1988)		
1	Phenitoin, 2 mg (0.04 ml)	5♀
2	UH-AC 62 XX, 2 mg (0.04 ml)	5♀
3	Placebo (0.04 ml)	5♀
4	Untreated control	5♀

Results: The following table presents the results obtained from each experiment. **High variability in the data was noted. In some experiments, the positive control was not working properly. It is difficult to draw any conclusions based on the presented information.**

Group		Mean LN Weight (mg)			Mean Cell N° ($x10^{-5}$)			Lymphocyte Phenotype (%)		
		R (Injected)	L (Control)	Ratio	R (Injected)	L (Control)	Ratio	$CD4^+$ (inj/con)	$CD8^+$ (inj/con)	sIg^+ (inj/con)
Experiment 1: (9/22/1998)										
1	Phenitoin, 1 mg (0.02 ml)	4.52	2.4	1.88	48.2	7.4	6.5	48/54	22/22	18/17
2	UH-AC 62 XX 1 mg (0.02 ml)	2.5	2.2	1.14	10.0	2.8	3.6	52/58	23/24	19/12
3	Placebo (0.02 ml)	3.28	2.54	1.29	5.2	7.6	0.7	56/51	25/23	17/17
Experiment 2: (10/21/1988)										
1	Phenitoin, 1 mg (0.02 ml)	5.32	5.0	1.06	17.1	0.8	21.4	59/62	24/33	10/5
2	UH-AC 62 XX 1 mg (0.02 ml)	4.02	3.24	1.24	10.9	4.2	2.6	57/64	29/29	11/8
3	Placebo (0.02 ml)	6.8	3.32	2.05	4.0	10.0	0.4	67/63	31/28	6/7
Experiment 3: (10/26/1988)										
1	Phenitoin, 1 mg (0.02 ml)	3.86	1.82	2.12	37.4	7.0	5.3	51/61	23/26	25/22
2	UH-AC 62 XX 1 mg (0.02 ml)	2.6	2.5	1.04	9.0	10.4	0.9	60/62	23/25	15/13
3	Placebo (0.02 ml)	2.8	2.7	1.04	15.9	9.6	1.7	58/60	24/25	14/13
4	Untreated control	2.4	3.5	0.69		12.1		ND	ND	ND
Experiment 4: (11/8/1988)										
1	Phenitoin, 2 mg (0.04 ml)	7.2	4.3	1.67	126.0	5.7	22.1	ND/62	19/19	34/19
2	UH-AC 62 XX, 2 mg (0.04 ml)	2.5	2.6	0.96	13.0	9.5	1.4	57/64	22/24	15/12
3	Placebo (0.04 ml)	2.6	1.7	1.53	8.2	8.2	1.0	58/60	23/24	21/23
4	Untreated control	1.8	2.8	0.64		8.5		64	28	13

ND = Not Determined.

2.6.2. *PHOTOTOXICITY*

The following study reports were submitted but not reviewed.

1. U92-0610 UH-AC 62 XX: Comparative in vitro determination of the phototoxic activity of different non-steroidal anti-inflammatory compounds. (Vol. 2.038, p 204)
2. U94-0315 Photosensitization test of UH-AC 62 XX Cresa 1% after repeated epidermal treatment to guinea pigs. (Vol. 2.038, p 269)

2.6.3. *RED CELL HEMOLYSIS TEST*

The following study reports were submitted but not reviewed.

1. U89-0235 Report on a hemolysis test with the preparation UH-AC 62 XX Ampullen 20 mg/2 ml. (Vol. 2.038, p 308)
2. U81-0062 Report on a hemolysis test with the preparations UH-AC 62 XX ampoules. (Vol. 2.038, p 315)
3. U85-0059 Report on a hemolysis test with the preparation UH-AC 62 XX ampoules 20 mg/2 ml. (Vol. 2.038, p 319)
4. U85-0743 Report on hemolysis test with UH-AC 62 XX ampoules, 30 mg/ml. (Vol. 2.038, p 323)
5. U92-0803 Report on a hemolysis test with the preparation UH-AC 62 XX ampoules 15 mg/1.5 ml vs. competitive preparations. (Vol. 2.038, p 328)
6. U93-0552 Report on a hemolysis test with the preparations UH-AC 62 XX ampoules 15 mg/1.5 ml vs. competitive preparations. (Vol. 2.038, p 337)

2.6.4. *VASCULAR TOLERANCE*

The following study reports were submitted but not reviewed.

1. U81-0060 Study of substance UH-AC 62 XX (ampoules) for intravenous tolerance. (Vol. 2.039, p 1)

2. U84-1030 We compared the intravenous tolerability of UH-AC 62 XX ampoules with that of placebo ampoules. (Vol. 2.039, p 3)
3. U84-0130 Study of the parenteral tolerance of substance UH-AC 62 XX in dogs. (Vol. 2.039, p 5)
4. U88-0181 Plasma level measurements of UH-AC 62 XX as part of a parenteral tolerance study (No. 06K/83) in the dog. (Vol. 2.039, p 45)
5. U89-0174 Testing of UH-AC 62 XX injection solution, preparation 20 mg/2 ml, for intra-arterial tolerance in the rabbit. (Vol. 2.039, p 56)
6. U82-0075 Study of UH-AC 62 XX ampoule solution for intra-arterial tolerance in the rabbit. (Vol. 2.039, p 66)
7. U86-0890 Study of UH-AC 62 XX ampoule solution (20 mg/2mL) for intra-arterial tolerance in the rabbit. (Vol. 2.039, p 74)

2.6.5. SUBCUTANEOUS AND MUSCULAR TOLERANCE OF UH-AC 62 XX

The following study reports were submitted but not reviewed.

1. U93-0417 UH-AC 62 XX Local tolerance after single paravenous injection in rats. (2.039, p 82)
2. U81-0667 UH-AC 62 XX, UH-AC 62 MU Injection tolerability of preparations ZK 74/15, ZK 73/112, and ZK 74/110 after subcutaneous administration in rats. (Vol. 2.039, p 103)
3. U93-2113 UH-AC 62 XX (meloxicam): Subcutaneous tolerance test after single administration to rabbits. (Vol. 2.039, p 107)
4. U91-0923 Intramuscular tolerance test of UH-AC 62 XX in rabbits by single administration. (Vol. 2.039, p 135)
5. U81-0063 Tolerance of UH-AC 62 XX solution following intramuscular injection in rabbits. (Vol. 2.039, p 165)
6. U84-0892 Intramuscular tolerance of UH-AC 62 XX ampoules with that of placebo ampoules. (Vol. 2.039, p 176)
7. U89-0173 Intramuscular tolerance test of UH-AC 62 XX in rabbits. (Vol. 2.039, p 193)
8. U93-2114 UH-AC 62 XX (meloxicam): Intramuscular tolerance test of UH-AC 62 XX compared to piroxicam and diclofenac after single administration to rabbits. (Vol. 2.039, p 216)
9. Rectal Irritation
10. U89-0125 Rectal tolerance test of UH-AC 62 XX in rabbits. (Vol. 2.039, p 247)
11. U92-0261 Rectal tolerance of UH-AC 62 XX by multiple administration in rabbits. (Vol. 2.039, p 263)

2.6.6. OCULAR IRRITATION

The following study reports were submitted but not reviewed.

1. U90-0114 Local mucosal tolerance of UH-AC 62 XX eye-drops after single administration in the rabbit eye. (Vol. 2.039, p 295)

2. U90-0244 Local mucosal tolerance of UH-AC 62 XX eye drops after multiple instillation in the rabbit eye. (Vol. 2.040, p 1)
3. U91-0760 Multiple dose local tolerability study of NSAID eye drops in the rabbit eye. (Vol. 2.040, p 22)
4. U92-0787 Examination of UH-AC 62 XX eye drops on local anesthetic effects in the rabbit eye. (Vol. 2.040, p 54)
5. U93-0196 4 weeks local ocular tolerance study of UH-AC 62 XX eye drops by instillation into the conjunctival sac of rabbits. (Vol. 2.040, p 81)
6. U93-0250 Acute eye irritation study of UH-AC 62 XX cresa (1%) by instillation into the conjunctival sac of rabbits. (Vol. 2.041, p 1)

2.6.7. SKIN IRRITATION

The following study reports were submitted but not reviewed.

1. U90-0239 Investigation of the dermal tolerance of UH-AC 62 XX Gel with multiple administration in rabbits. (Vol. 2.041, p 26)
2. U93-0680 Local toxicity study of the final formulation of UH-AC 62 XX cresa by epicutaneous administration for 4 weeks to rabbits with intact and abraded skin. (Vol. 2.041, p 77)

2.7. TOXICOLOGY OF THE STARTING MATERIAL 2,5-AMTH

2.7.1. ACUTE AND REPEATED DOSE TOXICITY

2.7.1.1. U93-0278 Acute oral toxicity test of "AMTH" in rats. (Vol. 2.041, p 309)

Report Nº: U93-0278
Study Nº: 10-04-1328/00-92
Study Aims: To determine the acute toxicity of the chemical intermediate 2-amino-5-methylthiazole of UH-AC 62 XX following single oral administration to rats followed by a 14-day observation period.
Compound:
Vehicle:
Dose and Route:
Animal: Wistar rats, (SPF Crb), weighing 208-243 g for ♂ and 158-197 g for ♀, 5/sex/group.
Study Site:
Study Date: 9/24/1992 - 10/30/1992
In-Life Observation: 14 days
GLP/QAC Compliance: Yes (OECD)
Study Design: Groups of 5/sex rats were orally dosed with 500 or 1000 mg/kg of AMTH and observed for 14 days. Body weights were determined on Days 0, 7, and 14. Necropsy was performed on all surviving animals (Day 14) or rats were found dead. LD_{50} values were calculated by the linear interpolation.

Results:

- Clinical Signs and Mortality - There were 10 deaths (1♀ @ 500 and 4♂+5♀ @ 1000 mg/kg) and all deaths occurred within 24 hr post dosing. Severe toxicity were observed at 10 min post dosing including signs of ↓ activity, ↑ pain reactions, ↓ body and abdominal tone, ↓ ear and plantary reflex, ↓ respiratory rate, ↓ reaction to noise, piloerection, ↑ salivation, ↑lacrimation, and abdominal or sqatting position. Some of these observed signs persisted upto 48 hr post dose. The calculated LD_{50} values for ♂ and ♀ were ~812.5 and ~687.5 mg/kg, respectively.
- Body Weights - Weight gains were normal for all surviving animals.
- Necropsy Findings - The major gross findings were redness of the renal pelvis and medulla, redness of the glandular stomach or the gastric mucosa.

2.7.1.2. U96-2545 2-amino-5-methylthiazole (AMTH): single dose toxicity study (ALD_{50}) in rats by dermal administration. (Vol. 2.041, p. 336)

Study Nº: 96B033
Report Nº: U96-2542
Study Aims: To determine the acute dermal toxicity of the chemical intermediate 2-amino-5-methylthiazole of UH-AC 62 XX to induce following single administration to rats followed by a 14-day observation period.
Compound:
Dose and Route:
Animal: 5/sex albino rats. (SPF), 53 days old, weighing 176-236.7 g.
Study Site:
Dosing Date: 5/7/1996

In-Life Observation: - 14 days
GLP/QAC Compliance: Yes

Study Design: AMTH (2g), was wetted with water (2 g) and evenly applied to the shorn dorsal skin with an elastic bandage and tapes. The plasters were removed 24 hr following application. All animals were observed 2x/day for clinical signs for 14 days. Body weights were recorded on Days 1 (Pre-R), 2, 3, 4, 7, and 14. Necropsy was performed on all animals at the end of the study (Day 14). Histopathological evaluations were not performed.

Results:

- Cinical Observations - No deaths occurred. Decreased body temperature and signs of sedation, prone position and piloerection were observed within 7 hr after local application of AMTH. These observations were gone by 24 hr after removal of plaster containing AMTH. Mean body temperature changes are shown in the following table.

Sex	Body Temperature (°C) at Various Time Points Post Dosing			
	4 hr	20 hr	27 hr	50 hr
♂	30.98	36.6	37.66	37.62
♀	30.28	36.04	36.3	37.7

- Body weight losses were noted in ♂ during Days 2→4 and ♀ during Days 2→7 as shown in the following table.

Sex	Mean Body Weight (g) at Various Time Points Post Dosing					
	Day 1	Day 2	Day 3	Day 4	Day 7	Day 14
♂	229.5	206.4	207.6	217.4	239.7	287.8
♀	182.4	165.9	161.6	167.2	180.8	204.8

- Necropsy - No gross lesions were identified during necropsy.

2.7.1.3. U96-2542 AMTH: repeated dose toxicity study in rats by oral administration (gavage) over a period of 4 weeks. (Vol. 2.042, p 1)

Study N°: 96B040
Report N°: U96-2542
Study Aims: To determine the oral toxicity of the chemical intermediate 2-amino-5-methylthiazole of UH-AC 62 XX following a 4-week repeated administration to rats.
Compound:
Vehicle:
Dose and Route:
Dosing duration: 4-week
Animal: (SPF) rats, 43 days old, weighing 208.6-231.0 g for ♂ and 160.1-178.8 g for ♀, 5-10/sex group.
Study Site:
Dosing Date: 5/14-6/10/1996
In-Life Observation: 5/14/1996 -7/22/1996
GLP/QAC Compliance: Yes (OECD)

Study Design: Groups of 5-10/sex rats were orally dose with vehicle, 4, 20, or 100 mg/kg/day of AMTH 14 days as shown in the following table. Five/sex from Group 0 and 3 were allowed to have a 6-week recovery phase.

Group	Treatment	Dose (mg/kg/day)	Dosing Vol. (ml/kg)	Dosing Duration	Nº of Animals
G 0	Vehicle Control	0	10	4-week with a 6-week recovery phase	10/sex
G 1	AMTH	4.0	10		5/sex
G 2		20.0	10		5/sex
G 3		100.0	10		6/sex*

* 5/sex from Groups 0 and 3 were allowed to have a 6-week recovery phase.

The following observations were conducted.

- Clinical Signs and Mortality - 2x/day.
- Body Weights and Food/H_2O consumption - 1x/week
- Clinical Pathology (Hematology and Clinical Chemistry) - Weeks 4, 6 (recovery phase), and 10 (recovery phase).
- Necropsy and Pathology - Weeks 4 and 10 (recovery phase).
  Organ Weights: The following organs from each animal were weighed: heart, lungs, liver, spleen, thymus, brain, pituitary, thyroid, kidneys, adrenals, gonads, and prostate (post-fixation).
  Gross and Histopathology: The following listed organs were collected from each animal and preserved in [redacted] Sections from these organs were subjected to microscopic examination.

Heart	Kidneys	Pancreas	Pituitary	Harderian Gland			Urinary Bladder	
Lungs	Adrenals	Brain	Thymus	Mesenteric Lymph Nodes			Femur	sternum
Liver	Esophagus	Eyes w/ Optic Nerve*		Lymph Node Neck Region			Mammary Gland (Females)	
Spleen	Stomach	Thyroid/Parathyroid Glands		Epididymides	Seminal Vesicles		Skeletal Muscle	
Small Intestine (Duodenum, Jejunum, Ileum)		Parotid Salivary Glands		Prostate	Testes		Tongue	
		Submandibular Glands		Uterus	Ovaries	Vagina	Trachea	
Large Intestine (Cecum, Rectum, Colon)		Sublingual Salivary Glands		Bone Marrow			Aorta	Skin
		Spinal Cord		Peripheral Nerve (Sciatic)			Macroscopic Lesions	

* Both eyes were fixed with Davison's solution.

Results:

- Clinical Signs and Mortality - No deaths occurred. Sedation and rough coat were major clinical observations. No abnormal behavior or clinical signs were noted during the recovery phase.
- Body Weights and Food Consumption - Lower mean weights (♂: ↓9-23%, Weeks 1→10; ♀: ↓5-15%, Weeks 2→10) with reduced cumulative weight gains (♂: ↓37%; ♀: ↓41%) and food consumption (♂: ↓8-42%, Weeks 1→9; ♀: ↓7-33%, Weeks 1→10) was noted in the high-dose group. Mid-dose animals also showed a reduction in food intake during Week 1/2 (♂: ↓7-14%; ♀: ↓4-7%).
- Hematology and Clinical Chemistry - The major findings in hematology and serum chemistry are shown in the following table.

Dose (mg/kg/day)	RBC ($10^6/\mu l$)		Hb (g/100 dl)		Ht (Vol.%)		Reticulocyte (N°/1000)		WBC ($10^3/\mu l$)		Lymphocyte ($10^3/\mu l$)		Platelet ($10^3/\mu l$)		TPT (Sec)	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
0	8.0	7.7	16.1	15.6	8.0	7.7	16.1	15.6	9.6	5.2	8.7	4.6	769.2	794.1	19.3	17.8
4	7.6	7.7	15.7	15.6	7.6	7.7	15.7	15.6	8.2	5.8	7.8	5.3	655.0	914.2	20.0	17.9
20	7.9	7.4*	16.0	15.0	7.9	7.4*	16.0	15.0	8.2	6.8	7.6	5.9	698.4	905.8	19.9	17.7
100	7.7	7.0*	15.8	14.5*	7.7	7.0*	15.8	14.5*	5.9*	4.1	5.5*	3.7	583.8*	657.1	22.5*	20.1*
0 (Recovery)	8.3	8.0	17.5	17.2	8.3	8.0	17.5	17.2	11.8	5.4	10.9	4.7	758.0	757.0	19.7	17.7
100 (Recovery)	7.9	7.7	16.7	16.3	7.9	7.7	16.7	16.3	11.4	4.8	9.9	4.3	743.2	753.4	20.4	18.2

Dose (mg/kg)	LAP (U/l)		CHE (U/l)		Bilirubin (μmol/l)		Glucose (μmol/l)		Cholesterol (mmol/l)		Glycerol (mmol/l)		BUN (mmol/l)		Creatinine (μmol/l)	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
0 (control)	26.4	24.4	144.6	678.9	1.3	1.6	8.5	7.9	1.6	1.8	1.9	1.6	9.1	8.8	42.3	43.6
4	24.2	24.4	192.8	538.8	1.2	1.0	8.5	8.0	1.7	2.0	1.8	1.1	9.6	8.6	42.2	42.9
20	24.0	24.7	136.8	520.0	1.4	1.2	7.7	7.7	1.8	2.0	1.7	1.4	10.6	8.8	42.6	41.4
100	37.4*	29.2*	264.2*	603.2	2.2*	1.5	7.3*	6.6*	2.9*	2.8*	0.7*	0.8	16.1*	14.7*	52.2*	56.0*
0 (Recovery)	24.5	22.6	188.0	755.4	1.0	1.0	7.9	8.6	1.8	2.0	2.2	2.4	8.3	7.3	43.9	48.4
100 (Recovery)	26.5	25.4	164.4	928.6	0.9	0.7	8.4	9.0	1.3*	1.8	1.2	1.4	7.3	8.2	47.8	50.9

* $p \leq 0.01$

- Necropsy -

  Organ Weights: Significant differences in the relative (to body weight) organ weights were observed between substance-treated and control groups:

  Heart: 100 mg/kg - ♂, ↓8%; ♀, ↓22%.

  Lungs: 100 mg/kg - ♂, ↑18%.

  Thymus: 100 mg/kg - ♂, ↓ 40%; ♀, ↓55%.
  100 mg/kg (Recovery Phase) - ♂, ↓42%.
  20 mg/kg - ♂, ↓ 68%; ♀, ↓21%.

  Spleen: 100 mg/kg - ♂, ↓51%; ♀, ↓35%.

  Adrenals: 100 mg/kg - ♂, ↓12%; ♀, ↓22%.

  Pituitary: 100 mg/kg - ♂, ↑78%; ♀, ↑14%.

  Thyroid: 100 mg/kg - ♂, ↑126% ; ♀, ↑167%.
  100 mg/kg (Recovery Phase) - ♂, ↑60% ; ♀, ↑51%.

  Gross and Histopathology: No remarkable gross pathological lesions were seen. Compound-related histopathological alterations were found in the pituitary gland, thyroid gland, adrenal cortex, thymus, liver, lungs and spleen. The incidence of major histopathology findings is shown in the following table.

MICROSCOPIC FINDINGS Organ/Lesions		Dose (mg/kg/day)*									
		0		4		20		100		100 (R)	
		♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Pituitary	Depiction of Acidophils	0/5	0/5	0/5	0/5	0/5	0/5	5/5	5/5	0/5	0/5
	Hyperplasia of Basophils	0/5	0/5	0/5	0/5	0/5	1/5	5/5	4/5	0/5	0/5
Thyroid	Follicular Cell Hypertrophy	0/5	0/5	0/5	0/5	0/5	2/5	5/5	5/5	0/5	0/5
	Follicular Cell Hyperplasia	0/5	0/5	0/5	0/5	0/5	0/5	5/5	5/5	0/5	0/5
	Follicle Enlargement	0/5	0/5	0/5	0/5	0/5	0/5	0/5	0/5	5/5	5/5
Adrenal Cortex	Atrophy	0/5	0/5	0/5	0/5	0/5	0/5	4/5	0/5	0/5	0/5
Thymus	Involution/Atrophy	0/8[b]	0/5	0/5	0/5	1/5	2/5	5/5	5/5	0/5	0/5
	Cortical Single Cell Necrosis	0/8[b]	0/5	0/5	0/5	0/5	0/5	2/5	0/5	0/5	0/5
Liver	Hepatocellular Hypertrophy	0/6[b]	0/7[b]	0/5	0/4	2/5	0/5	4/5	1/4	0/5	0/5
Lungs	Foam Cell Accumulation	0/5	1/7	1/5	0/4	0/5	0/5	4/5	2/4	3/5	1/5
Spleen	Red Pulp Depletion	0/5	0/5	0/5	0/4	0/5	0/5	4/5	0/4	0/5	0/5

* N° of affected animals/total N° animals in the group.
[b] Animals of the recovery group were included.

2.7.2. *SKIN AND OCULAR IRRITATION*

2.7.2.1. U94-2059 UH-AC 62 XX: dermal tolerance study of the chemical intermediate 2-amino-5-methylthiazole after single administration to rabbits. 21 March 1994. (Vol. 2.044, p 1)

Report Nº: U94-2059
Study Nº: 27 S
Study Aims: To determine the dermal tolerance of the chemical intermediate 2-amino-5-methylthiazole of UH-AC 62 XX following single administration to rabbits followed by a 7-day observation period.
Compound:
Dose and Route:
Animal: 3♂ and 3♀ albino rabbits, 113-155 days of age, weighing 3.24-3.46 kg.
Study Site:
Dosing Date: 1/18/1994
In-Life Observation: 7 days
GLP/QAC Compliance: Yes (OECD)
Study Design: Test compound was wetted with water and evenly applied to three (263.2 mg/each plaster) sites on the shorn dorsal skin. The plasters were removed 3 min, 1, and 4 hr following application. The skin was evaluated for irritation (erythema and formation of eschar, formation of edema, and necrosis) at 1, 24, 48 and 72 hr after removal of plaster and scores (Draize scales) were recorded. All animals were observed 2x/day for clinical signs for a period of 7 days. Food consumption was determined by visual inspection. Necropsy and microscopic examinations were performed.

Results: There were no visible skin changes noted. Therefore, 2-amino-5-methylthiazole, an intermediate of UH-AC 62 XX, was not a rabbit skin irritant under the current testing condition.

2.7.2.2. U94-2076 2-amino-5-methylthiazole: acute eye irritation test after single administration to rabbits. 25 April 1994. (Vol. 2.044, p 21)

Report Nº: U94-2076
Study Nº: 26 S
Study Aims: To determine the acute ocular irritation potential of the chemical intermediate 2-amino-5-methylthiazole of UH-AC 62 XX in rabbits.
Compound:
Dose and Route:
Animal: 2♂ and 2♀ albino rabbits, 159-166 days of age, weighing 4.16-4.54 kg.
Study Site:
Dosing Date: 12/7/1993
In-Life Observation: 72 hr
GLP/QAC Compliance: Yes (OECD)
Study Design: Test compound 2-amino-5-methylthiazole in 0.1 cm^3 (~20 mg) was placed into the conjunctival sac of right eye. The left eye served as control. Ophthalmoscopic examinations of cornea, iris, conjunctiva and lids were conducted at 1, 6, 24, 48, and 72 hr post-dose with a hand-held slit lamp. Scores of ocular irritation were recorded according to OECD Guideline 405. All rabbits were observed 2x/day for clinical signs. Food consumption was determined by visual inspection. Necropsy and microscopic examinations were performed.

Results: Moderate to severe redness of conjunctiva with swelling of the lids was observed in all treated eyes at 1, 6, and 24 hr post dose. All observed ocular changes subsided by 72 hr post dose.

Therefore, 2-amino-5-methylthiazole, an intermediate of UH-AC 62 XX, was an irritant to rabbit eyes under the current testing condition.

2.7.2.3. U93-0277 Guinea pig maximization test of skin sensitization with "AMTH". 11 November 1992. (Vol. 2.044, p 42)

Report Nº: U93-0277
Study Nº: 10-05-1329/00-92
Study Aims: To assess the contact sensitizing potential of AMTH in the guinea pigs.
Compound:
Dose and Route:
Vehicle:
Positive Control:
Animals: guinea pig( ) (SPF), weighing 376-500 for ♂ and 381-499 g for ♀. 10/sex.
Study Site:
Study Date: 10/7/1992 - 11/6/1992
GLP/QAC Compliance: Yes
Study Designs: The below table depicts the detailed treatment schedules for the control and test groups.

Day	Treatment Schedule	Skin Induction Site (4 cm x 6 cm area)		
		Anterior Site	Medial Site	Posterior Site
CONTROL GROUP (10 ANIMALS)				
1	Intradermal Injection	0.1 ml FCA:H_2O=1:1	0.1 ml Na-CMC	0.1 ml Na-CMC in FCA(1:1)
7	Topical Pre-treatment	10% w/w Sodium Lauryl Sulfate suspension in Vaseline (50% v/v)		
8	Topical Induction	Vaseline secured by an overwrap with tape for 48 hr.		
22	Challenge	Vaseline secured by an overwrap with tape for 24 hr.		
TEST GROUP (20 ANIMALS)				
1	Intradermal Injection	0.1 ml FCA:H_2O=1:1	0.1 ml of 1% AMTH in Na-CMC	0.1 ml of 1% AMTH in FCA/H_2O (1:1)
7	Topical Pre-treatment	50% w/w Sodium Lauryl Sulfate suspension in Vaseline (50% v/v)		
8	Topical Induction	50 w/w AMTH in Vaseline secured by an overwrap with tape for 48 hr.		
22	Challenge	50 w/w AMTH in Vaseline secured by an overwrap with tape for 24 hr.		

The challenge sites were examined at 24 and 48 hr following challenge application patch removal. The reactions were scored according to a 5-point scale: 0 = no erythema/edema; 1 = very slight erythema/edema; 2 = well define erythema and slight edema 3 = moderate to severe erythema/edema (raise ~1 mm); 4 = intense redness to slight eschar formation and severe swelling (raised >1 mm).

Results: Results from a pilot study showed that 2.5% and 5% AMTH in Na-CMC and Freund's complete adjuvant caused skin irritation (slight to extreme redness) at 48 hr post intradermal injection and 50% AMTH in Vaseline did not elicit skin reaction at 48 hr post skin application. Thus, in the definite study, the sponsor employed 1% AMTH in Na-CMC and Freund's complete adjuvant for intradermal injection and 50% AMTH in Vaseline for dermal application and topical challenge. No animals had reaction to the challenge application of either control material or AMTH. Therefore, AMTH was not a skin sensitizer under the current testing condition.

2.7.3. GENOTOXICITY

2.7.3.1. U94-2080 Mutagenicity study with 2-amino-5-methylthiazole in the *S. Typhimurium* reverse [redacted] 19 April 1994. (Vol. 2.044, p 64)

Report Nº: U94-2080
Study Nº GEN TOX 07/94
Study Aims: To assess the mutagenic potential of 2-amino-5-methylthiazole using [redacted]

Compound:
Dose:
Vehicle Control:
Indicator Cells:

S9 Mix:
Positive Control:

Exposure Time: 48 hr at 37°C (72 hr for TA102)
Study Location: [redacted]
Study Date: 1/25/94 - 2/4/94
Compliance with GLP/QAU: Yes [redacted]

Results: Slight dose-dependent increases (↑10-84%) in the mutation rates were observed in the tester strains TA 100 and TA 102 at doses ≥1000 μg/plate under the condition with or without activation S9.

2.7.3.2. U96-2511 Mutagenicity study for chromosomal aberrations in human lymphocytes in vitro with 2-amino-5-methylthiazol (2,5-AMTH). 08 October 1996. (Vol. 2.044, p 99)

Report Nº: U96-2511
Study Nº: 96B069
Study Aims: To assess the potential of 2-amino-5-methylthiazole to induce chromosomal aberrations in human lymphocytes

Compound:
Dose:
Vehicle Control:
Indicator Cells:
S9 Mix:
Positive Control:
Exposure Time:
Study Location: [redacted]
Study Date: 7/22/1996-9/03/1996
Compliance with GLP/QAU: Yes [redacted]

Results: AMTH, at a concentration 1500 μg/ml, in the absence of activation S9 caused high toxicity to PHA-stimulated human lymphocyte with a 5% of viability. Data revealed a dose-dependent

increase in the incidence of cells with aberration in the presence or absence of activation mixture as shown in the following table.

Compound (μg/ml)		Mitotic Index - %	Cells Scored	Type and Incidence of Aberration							Cells with Aberration			
											Total		%	
				g	ctb	cte	ace	td	csb	cse	Incl Gap	Excl Gap	Incl Gap	Excl Gap
Without Metabolic Activation (-S9)														
(-)Control	DMSO	100	100	1	1						2	1	2	1
(+)Control	ADR 0.05	72	100	5	7	1	8		1		18	13	18	13
AMTH	50	73	100				1				1	1	1	1
	250	52	100	2	1		2				5	3	5	3
	500	51	100		3						3	3	3	3
	750	41	81	4	5		2	1	3		15	11	18.5	13.6
	1000	12	35	Not Evaluated										
With Metabolic Activation (+S9)														
(-)Control	DMSO	100	100						1		1	1	1	1
(+)Control	CP 7.0	50	83		12	3	1		2		18	18	21.7	21.7
AMTH	250	88	100	1							1	0	1	0
	750	73	100				1				1	1	1	1
	1500	61	100	5	3		2		1		11	6	11	6

g = chromatid and chromosome gap; ctb = chromatid break; csb = chromosome break; ace = acentric fragment; td = terminal deletion.

2.7.3.3. U97-2477 Mutagenicity study in the rat bone marrow [redacted] after oral treatment with 2,5-AMTH (starting material of UH-AC 62 XX synthesis). 05 August 1997. (Vol. 2.044, p 136)

Report Nº: U97-2477
Study Nº: 97B037
Study Aims: To assess the potential of 2-amino-5-methylthiazole to induce micronuclei in the rat bone marrow polychromatic erythrocytes
Compound: [redacted]
Dose and Route:
Vehicle Control:
Positive Control:
Animals: 30♂ [redacted] (SPF) rats, 54 days old, weighing 219-255 g
Sampling Time: 24 hr post-Ⓐ for all dose and 48 hr post-Ⓐ for high dose group
Study Location: [redacted]
Study Date: 5/13/1997 - 6/19/1997
Compliance with GLP/QAU: Yes
Study Designs: Animals were randomly assigned to 5 dose groups as listed in the following table. All rats were monitored for signs of toxicity, moribundity, and mortality. Animals were sacrifice at 24 or 48 post single dose treatment and bone marrow smears were prepared. A total of 1000 polychromatic erythrocytes (PE) per animal were evaluated for micronucleated cells (MNE).

Compounds	Dose (mg/kg)	Nº of Rats Sacrificed	
		24 hr post-Ⓐ	48 hr post-Ⓐ
Vehicle Control	0	5	-
AMTH	20	5	-
	100	5	-
	500	5	5
Cyclophosphamide	30	5	-

Results: There were treatment-related and dose-dependent clinical signs of sedation, prone position, irregular breathing and dacryorrhea observed. High-dose group showed significantly lower PE ratios at 24 (↓51%) and 48 hr (↓54%) post dose, an indicative of myelotoxicity. A slight but dose-dependent increase in the incidence of MNE was seen and data are presented in the following table.

Groups	Dose (mg/kg)	Sampling Time (hr)	PE (%)	MNE (%)
Vehicle Control	0	24	29.1	0.1
AMTH	20	24	26.1	0.16
	100	24	25.1	0.18
	500	24	19.3	0.20
		48	13.3	0.20
Cyclophosphamide	30	24	14.1	0.76

2.7.3.4. U97-2502 Measurement of unscheduled (UDS) and replicative DNA synthesis (RDS) in rat liver in vivo/in vitro after oral treatment with 2,5-AMTH [redacted] 5 September 1997. (Vol. 2.044, p 160)

Report Nº: U97-2502
Study Nº: 97B095
Study Aims: To assess the potential of 2-amino-5-methylthiazole to induce unscheduled (UDS) and replicative DNA synthesis (RDS) in rat hepatocytes.
Compound: [redacted]
Dose and Route:
Vehicle Control
Positive Control:
Animals: ♂ [redacted] (SPF) rats, ~6 weeks old, weighing 169-228 g
Sampling Time: 24 hr post-Ⓡ for all dose and 48 hr post-Ⓡ for high dose group
Study Location: [redacted]
Study Date: 7/14/1997 - 8/12/1997
Compliance with GLP/QAU: Yes
Study Designs: Rats were randomly assigned to 3 dose groups as listed in the following table. All rats were monitored for signs of toxicity, moribundity, and mortality. Animals were sacrifice at 4 and 16 post single dose treatment and hepatocytes were prepared by a two-stage *in situ* perfusion of the liver. Isolated hepatocytes were cultured at a density of $1x10^5$ cells and pulsed with H^3-thymidine for a period of 18 hr. Then, cells were washed and processed for autoradiography.

Compounds	Dose (mg/kg)	Nº of Rats Sacrificed	
		4 hr post-Ⓡ	16 hr post-Ⓡ
Vehicle Control	0	2	2
AMTH	500	3	3
Dimethylhydrazine	80	1	1

Results: Marked treatment-related signs of toxicity with observations of sedation, prone position, irregular breathing and dacryorrhea were identified. Results showed that treatment of 500 mg/kg of AMTH did not increase the incidence of unscheduled or replicative (S-phase) DNA synthesis in primary rat hepatocytes.

3. ADME

3.1. ABSORPTION AND EXCRETION

3.1.1. SINGLE DOSE STUDIES OF THE PHARMACOKINETICS OF UH-AC 62 XX

3.1.1.1. U93-0146 Blood and plasma levels and excretion balance following an intravenous and oral dose of 10 mg/kg [^{14}C]UH-AC 62 XX in the mouse. 10 December 1992. (Vol. 2.049, p 184)

Study Nº: B118

Report Nº: U93-0146
Study Aims: To determine PK and bioavailability of UH-AC 62 XX in the mouse following iv and oral administration.
Compound: [redacted]
Dose and Route: [redacted]
Animals: ♂ & ♀ albino mice, [redacted] weighing 21-29 g, 5/sex/time point.
Study Date: 8-10/1988 to 8/1992
Blood Sampling: oral, 0.5, 1, 2, 3, 5, 8, and 14 hr post-dose; iv, 5 and 30 min and 1, 2, 3, 5, 8, and 24 hr post-dose.
Urine Sampling: 0-4, 4-8, 8-24, 24-48 and 48-72 h post dosing.
Feces: 0-4, 4-24, 24-48, and 48-72 hr.
Radioactivity Determination: [redacted]
UH-AC 62 XX Determination: HPLC; limit of quantitation [redacted]

Results: The following table shows mean plasma PK parameters in mice following a single oral or iv dose of [^{14}C]UH-AC 62 XX. The bioavailability [(AUC_{oral}/AUC_{iv})x100] was 94%. The majority of radioactivity was eliminated (0-72 hr) through urine (40%) and feces (42%). Following oral administration of [^{14}C]UH-AC 62 XX, higher radioactivity was detected in the plasma than blood and the predominant radioactivity was derived from parent compound.

PK Parameters	Oral			IV
	♂ + ♀	♂	♀	♂ + ♀
C_{max} (µg eq/ml)	18.14	16.7	19.35	36.63
T_{max} (hr)	0.7	0.6	0.6	
$AUC_{0-\infty}$ (µg eq•hr/ml)	60.74	44.36	69.65	64.69
$MRT_{0-\infty}$ (hr)	3.89	2.72	3.55	3.02
$T_{1/2}$ (hr)	4.76	1.8	2.39	6.41
V_{ss} (l/kg)				0.47
Clp (ml/min•kg)	2.74			2.58
F (AUC_{oral}/AUC_{iv})	0.94			

3.1.1.2. U87-0171 UH-AC 62 XX: Excretion and metabolic pattern found in the urine and bile of male and female rats after PO and ID administration. 04 February 1987. (Vol. 2.049, p 236)

Study Nº: ADME 43/86
Report Nº: U87-0171
Study Aims: To determine excretion and metabolic profile in urine and bile following oral and intra-duodenal (id) administration to rats.
Compound: [redacted]
Dose and Route: [redacted]
Animals: ♂ & ♀ rats, [redacted] weighing 200-250 g, 3/sex for metabolite pattern study and 8♂ for dose linearity study.
Study Date: Not stated.
Urine Sampling: 0-4, 8-24, 24-48 and 48-72 hr post doing.
Feces Collection: 0-4, 4-24, 24-48, 48-72 and 72-96 hr.
Bile Sampling: 0-2, 2-4, and 4-6 hr post dose
Metabolic Profile Determination: [redacted]

Results:

- **Excretion and Metabolic Profiles in Urine and Feces** - Similar metabolic profiles in urine from ♂ and ♀ rats as identical peaks but in different quantities were obtained during radiochromatographic analysis. Unchanged parent drug, [^{14}C]UH-AC 62 XX, was not detectable in the urine from male rats. However, ~7% of unchanged parent drug was detected in the accumulative (0-48 hr) urine sample obtained from female rats. In addition, male urine samples contained higher amount of metabolite 5. Mean percent radioactivity dose excreted in the urine and feces after oral administration of [^{14}C]UH-AC 62 XX are listed in the following table. There was a sex difference in the excretion of the radioactivity into urine and data showed that ♂ eliminated drug via urine faster than ♀. In contrast, no sex-difference in the elimination of drug via feces was noted.

Dose (mg/kg)	Time	Sex	N	Mean (±SD) % Dose Excreted		
				Urine	Feces	Total
1	0-72 hr	♂	3	63.8	27.2	91.0 ± 8.27
		♀	3	43.5	25.7	69.2 ± 4.17
10	0-96 hr	♂	8	76.3	22.0	98.3 ± 4.63

- **Excretion and Metabolic Profiles in Bile** - The following table summarized mean % radioactivity of the dose excretion in the bile following id administration of 1 mg/kg [^{14}C]UH-AC 62 XX. An apparent gender difference in bile excretion was noted. Radiochromatographic analysis showed similar peaks in both male and female rats. However, greater amounts of unchanged parent compound (2.6x) and metabolite 8B (2x) were present in bile obtained from ♀ rats.

Time (hr)	N	% Dose Excreted in Bile	
		♂	♀
2	4	1.82	1.26
4	4	5.00	2.75
6	4	7.88	4.25

3.1.1.3. U87-0431 UH-AC 62 XX Pharmacokinetics in the rat. 05 June 1987. (Vol. 2.049, p 281)

Study Nº: ADME 4/87
Report Nº: U87-0431
Study Aims: To determine PK, excretion and metabolic profile in the urine and plasma following oral and iv administrations of [^{14}C]UH-AC 62 XX to rats.
Compound:
Dose and Route:
Animals: ♂ & ♀ rats, (SPF), weighing 200-240 g;
Pregnant (GD 18) albino rats, (SPF), and natural gray
Study Date: Not stated.
Blood Collection: 10 and 30 min, 1, 2, 4, 6, 8, 24, 48, 72, 144, 168 and 192 hr post-dose.
Urine Sampling: 0-8, 8-24, 24-48 and 48-72 hr post doing.
Feces Collection: 0-24, 24-48, 48-72 and 72-96 hr.
Bile Sampling: 0-2, 2-4, and 4-6 hr post dose. For determination of enterohepatic circulation, the bile was collected from a group of 3 animals over 6 h after iv administration of 1 mg/kg [^{14}C]UH-AC 62 XX. The bile was pooled and radioactivity was determined. Then 1 ml of the pooled bile was given to the another group of

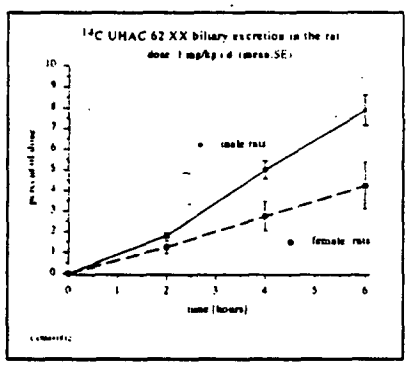
animals by id. The bile secreted by these animals was collected over 6 h for the radioactivity determination.

Results:

- Blood Levels and PK Parameters - The mean PK parameters (n=5) for [^{14}C]UH-AC 62 XX in blood following oral and iv administration of 1.0 mg/kg are presented in the following table.

Parameters	♂		♀	
	po	iv	p	iv
C_{max} (mg eq/l)	2.35	-	3.23	
t_{max} (hr)	4.4	-	6.8	
$AUC_{0-\infty}$ (μg eq•hr/ml)	83.3	70.9	201.0	217.0
$MRT_{0-\infty}$ (hr)	31.8	18.0	53.4	52.6
$t_{1/2}$ (hr)	49.9	13.4	52.4	36.8
Clp (l/hr•kg)	0.023	0.015	0.01	0.005
V_{ss} (l/kg)	0.257	-	0.244	-

- Distribution of Radioactivity in RBC/Plasma - About 1-10% of the radioactivity was distributed into RBC at 2, 8, and 24 hr post oral administration of 1 mg/kg [^{14}C]UH-AC 62 XX.
- Protein Binding - More than 99% of radoioactivity was bound to plasma proteins at 6 and 30 hr post a single oral dose of [^{14}C]UH-AC 62 XX. Data showed that acid metabolite, UH AC 110XX, did not displace the binding between the parent compound and plasma proteins by addition of 78.5 μg of UH AC 110XX to the plasma.
- Tissue Distribution - Measurement of the concentration of the radioactivity in the tissues and whole-body autoradiographs showed that the liver had highest radioactivity. Relative high radioactivity was detected in the blood, lungs, skin and kidneys. A lower concentration is detectable in the skeletal muscles and only slight traces of radioactivity was shown in the central nervous system. Data showed that [^{14}C]UH-AC 62 XX and its metabolites have no affinity for pigmented layers in the skin or eyes.
  Whole body autoradiographs of pregnant (GD 19) rats showed that distribution of radioactivity in the fetal skeletal muscle was higher than in the maternal muscle indicative of placental transfer of the drug.
- Excretion in Bile - Data from the kinetic study showed that the biliary excretion was not completed by 6 hr post iv and id administration. The cumulative (0-6 hr) % biliary excretion of radioactive dose in the ♂ and ♀ was 7.9% and 4.3%, respectiverly following in administration of 1 mg/kg of [^{14}C]UH-AC 62 XX as shown in the right figure, an indicative of gender difference.



- Urinary and Fecal Excretion - Cumulative urinary and fecal excretions of total radioactivity expressed as % dose following oral and iv administration of 1 mg/kg [^{14}C]UH-AC 62 XX are listed in the following table. Apparent gender difference in renal excretion was noted as ♂ had higher cumulative excretion of radioactive dose in the urine. In addition, ♀ had slower elimination rate as only 69% dose was eliminated at 72 hr post oral dosing while ♂ had 91% of total dose was eliminated during the same time period.

Time (hr)	iv						po					
	♂			♀			♂			♀		
	Urine	Feces	Total	Urine	Feces	Total	Urine	Feces	Total	Urine	Feces	Total
0-24	46.9	14.8	61.7	18.2	3.8	22.0	48.2	17.6	65.7	22.1	8.2	30.3
0-48	59.8	21.7	81.4	32.9	11.6	44.5	60.5	24.7	85.3	35.9	19.2	55.1
0-72	64.5	23.7	88.2	41.7	15.9	57.6	63.8	27.2	91.0	43.6	25.7	69.3
0-96	67.2	25.0	92.2	49.6	19.7	69.3	-	-	-	-	-	-

3.1.1.4. U88-0179 Investigations of the absorption of UH-AC 62 XX from the gastro-intestinal tract of the rat. 01 February 1988. (Vol. 2.049, p 350)

Study Nº: ADME 4/88
Report Nº: U88-0179
Study Aims: To determine absorption of UH-AC 62 XX by individual section of the intestine and the excretion of radioactivity in the bile.
Compound: [redacted]
Dose and Route: [redacted]
Animals: 5 albino rats
Study Date: Not stated.
Sampling: iv - 1, 9, 24, 48, and 96 hr and 12 and 16 days post does;
oral - 5, 9, 24, 48, and 96 hr and 12 and 16 days post does.
Radioactivity Determination: [redacted]

Results: Measurement the biliary excretion of radioactivity after application of 1 mg/kg of [^{14}C]UH-AC 62 XX into each segment of the GI tract was conducted. The cumulative elimination (0-6 hr) of the radioactivity in the bile were 4, 6, 7, and 12% of dose, respectively following administration of [^{14}C]UH-AC 62 XX into stomach, duodenum, ileum, and colon. Data suggested that absorption of UH-AC 62 XX occurred over a long section of the GI tract and only small amounts of UH-AC 62 XX were excreted via the bile.

3.1.1.5. U95-0278 Absorption, distribution and excretion after single and repeated administration of [^{14}C]-UH-AC 62 XX in rats. (Vol. 2.050, p 1)

Study Nº: NBIBC-9502
Report Nº: U95-0278
Study Aims: To determine absorption, distribution and excretion of UH-AC 62 XX following a single and repeated iv or oral administration of 1 mg/kg to rats.
Compound: [redacted]
Dose and Route: [redacted]
Animals: ♂ and ♀ rats [redacted] weighing 11.7-13.8 kg.
Study Date: Not indicated.
Blood Collection: single iv - 5, 15, 30 min and 1, 2, 4, 8, 24, 48, and 72 hr
single po -0.5, 1, 2, 4, 6, 8, 10, 21, 48, and 72 hr
repeated po - Day 1, 1, 4, 8 hr; Days 2, 3, 4, 5, 6, 7, 8, 10, and 12, 0 hr; Day 14, 0, 0.5, 1, 2, 4, 6, 8, 10, 24, 48, 72, 96, and 168 hr
Tissue Collection: ♂ po - 1, 4, 8, 24, 48, and 168 hr
♀ po - 1, 4, 48 hr
Urine and Fecal Sampling: 24-hr intervals up to 164 hr
Bile Collection: 0-1, 1-2, 2-3, 3-4, 4-6, 6-8, 8-24, and 24-48 hr via cannula. For determination of enterohepatic circulation, the bile was collected from 2♂ animals over 4 h after intra-duodenum administration via duodenum cannula of 1 mg/kg [^{14}C]UH-AC 62 XX. The bile was pooled and radioactivity was determined. Then

1 ml of the pooled bile was given to the another group of animals by id. The bile secreted by these animals was collected for the radioactivity determination in fractions of 0-1, 1-2, 2-3, 3-4, 4-6, 6-8, 8-24, and 24-48 hr.

Results:

- PK in Plasma - Mean (±SD) PK parameters of radioactive dose in plasma following a single oral or iv administration or repeated 14-day oral dosing of 1 mg/kg [^{14}C]UH-AC 62 XX to ♂ rats are presented in the below table. Slightly increased AUC and C_{max} values were noted in non-fasted rats. In addition, food also slightly delayed UH-AC 62 XX absorption as higher T_{max} value was noted in non-fasted animals.

Parameters	Single Dose			14-Day Repeated Oral Dosing
	Fasted		Non-fasted	
	iv (n=4)	po (n=5)	po (n=5)	
C_{max} (μg eq/ml)		3.23 ± 0.73	3.95 ± 0.47	7.12 ± 3.27
C_{max} (1-Dose) (μg eq/ml)				2.82 ± 0.91
C_{max} (14Doses) (μg eq/ml)				4.32 ±3.17
T_{max} (hr)		6.4 ± 1.7	7.6 ± 2.6	7.2 ± 3.0
$T_{½}$ (hr)	15.5 ± 5.3	14.5 ± 3.1	12.3 ± 3.8	17.4 ± 6.1
AUC_{0-72} (μg eq•hr/ml)	121.5 ± 65.3	83.3 ± 27.7	102.0 ± 41.4	
MRT (hr)	14.9 ± 6.0	17.8 ± 3.9	16.7 ± 5.0	
CL_{tot} (ml/min•kg)	0.17 ± 0.09			

- Radioactivity in Tissues - Data showed that the highest concentrations of radioactivity were detected in the GI tract, liver, plasma, blood, and kidney in the ♂ rats. High levels of radioactivity were seen in the lung and thyroid. T_{max} value for most tissues was 4 hr except the liver and kidney that had peak levels of radioactivity 8 hr after dosing. Similar tissue distribution patterns were noted for female rats. However, markedly higher levels of radioactivity were detected in the ♀, indicating that ♀ had a slower elimination rate than ♂.
- Urinary and Fecal Excretion - Mean cumulative excretion of radioactivity in the urine and feces following oral administration to ♂ and ♀ is summarized in the following table. Females had slower excretion of drug, although no gender differences in the patterns of excretion via urine and feces.

Period (hr)	Mean (±SD) % Radioactive Dose Excreted					
	♂			♀		
	Urine	Feces	Total	Urine	Feces	Total
0-24	41.25 ± 15.99	32.96 ± 11.51	74.21 ± 7.48	23.21 ± 10.19	27.46 ± 7.96	50.67 ± 13.91
0-48	50.05 ± 14.40	36.43 ± 11.86	86.48 ± 4.17	34.73 ± 9.15	33.90 ± 8.95	68.63 ± 15.07
0-72	53.73 ± 13.51	37.66 ± 12.04	91.40 ± 2.89	42.15 ± 7.10	37.21 ± 8.95	79.35 ± 12.92
0-96	55.45 ± 13.12	38.34 ± 12.17	93.79 ± 2.76	46.88 ± 5.29	39.02 ± 8.70	85.90 ± 10.22
0-168	56.73 ± 12.90	39.04 ± 12.36	95.77 ± 2.97	53.05 ±4.68	41.26 ± 7.92	94.30 ± 5.66

- Biliary Excretion - Biliary excretion of radioactivity was nearly completed in ♂ by 48 hr post iv administration. Mean cumulative biliary excretion of total radioactive dose was 19.8% in ♂ and 12.5% in ♀. Approximately 11% of radioactivity was excreted in the bile of ♂ rats following intra-duodenal injection of the pooled bile collected from donor rats that had received an iv dose of 1 mg/kg [^{14}C]UH-AC 62 XX.

3.1.1.6. U92-0124 Pharmacokinetics and bioavailability in beagle dogs following single intravenous, oral and subcutaneous administration of 0.2 mg/kg Metacam. (Vol. 2.050, p 66)

Study Nº: B43
Report Nº: U92-0124
Study Aims: To determine PK and absolute bioavailability of UH-AC 62 XX in dogs following a single dose of 0.2 mg/kg via oral , iv, or sc administration.

Compound:

Dose and Route:

Animals: 3♂ and 3♀ beagle dogs weighing 11.7-13.8 kg.

Study Date: 9/1991 - 11/1991

Results: Mean PK parameters after administration of single doses of 0.2 mg/kg of UH-AC 62 XX to dogs via the oral, intravenous and subcutaneous routes are shown in the following table.

Parameters	Oral		Intravenous		Subcutaneous	
	Mean	CV (%)	Mean	CV (%)	Mean	CV (%)
C_{max} (µg/ml)	0.464	12.7	-	-	0.734	15.9
T_{max} (hr)	7.5	110	-	-	2.5	74.8
$AUC_{0-\infty}$ (µg•hr/ml)	22.9	16.0	21.5	13.1	24.1	16.3
MRT_{ev} (hr)	40.0	21.9	34.8	23.6	35.0	13.1
$T_{1/2}$ (hr)	23.7	30.0	24.0	26.5	23.7	18.0
Clp (l/hr•kg)	0.009	14.7	0.01	13.0	0.008	17.1

3.1.1.7. U80-0052 The elimination kinetics of radioactivity following oral administration of [^{14}C]UH-AC 62 XX by gavage to sedated minipigs. (Vol. 2.050, p 102)

Study Nº: 114570

Report Nº: U80-0052

Study Aims: To determine PK parameters in pigs following oral administration.

Compound:

Dose and Route:

Animals: 3 ♂ minipigs

Study Date: Not stated.

Results: Approximately 83.5% of radioactive dose were recovered in 4 days. Mean cumulative (0-96 hr) urinary and fecal excretions were 28.5% and 52.5% of radioactive dose, respectively.

Parameters	Mean
C_{max} (µg eq/ml)	18.5
T_{max} (hr)	3.0
$T_{1/2}$ (hr)	4.5

3.1.1.8. U83-0067 Pilot study of improved formulations in the minipigs. (Vol. 2.050, p 178)

Study Nº: ADME 8/83

Report Nº: U83-0067

Study Aims: To compare PK parameters in pigs following administration of three different formulations of UH-AC 62 XX.

Compound:

Dose and Route:

Animals: ♂ minipigs, 3/group

Study Date: Not stated.

Results: Mean PK parameters for each formulation are shown in the following table.