2. **"Tube" was indicated as one of the organ parts preserved in [redacted] (Vol. 2.19, p 33). In some reports, both fallopian tubes and tubes were included in the histopathology list. What does the "tube" represent? The sponsor needs to provide an explanation for this particular organ.**
3. **The unit of reticulocyte count was stated as "0/00 of the erythrocytes" in the report (Vol. 2.19, p 25). What does the unit represent? Generally, the unit for reticulocyte count is expressed as % or Nº of reculocytes/1000 counted cells.**
4. **Several organs/tissues such as small intestine, large intestine, adrenal, thymus, etc., showed autolysis as stated in the report, an indicative of improper handling of tissue preservation during necropsy.**

These issues reflect inadequate preparation of NDA submission.

2.2.2.6. U88-0001 Chronic toxicity study on the substance UH-AC 62 XX in rats by oral administration over a period of 18 months. 10 April 1986. (Vol. 2.015, p 1)

U93-0492 Toxicokinetic monitoring of UH-AC 62 XX in rats at the end of a long term toxicity study (18 months) at daily oral doses of 1, 2, and 3.5 mg/kg (study no. 68 K). 30 March 1993. (Vol. 2.018, p 1)

Study Nº: 68 K (B168)
Report Nº: U88-0001 and U93-0492 (PK)
Study Aims: To determine the toxicity of UH-AC 62 XX following oral administration to rats for 18 months.
Compound: [redacted]
Dose and Route: [redacted]
Vehicle Control: [redacted]
Animal: Rats, [redacted] (SPF), 65-76 days old, weighing 160-180 g, 24/sex/group.
Study Site: [redacted]
Dosing Date: 1/24/1984 - 7/22/1985
Study Date: 1/3/1984 - 8/16/1985
GLP/QAC Compliance: Yes
Study Design:

Group	Compound	Dose (mg/kg)	Dose Vol. (ml/kg)	Dosing Duration	Nº of Animals
0	Vehicle Control	0	2.5	18-Month	24/sex
1	UH-AC 62 XX	1.0			24/sex
2		2.0			24/sex
3		3.5			24/sex

The following parameters were monitored.

- Clinical Signs and Mortality - 2x/day during Mondays → Fridays and 1x/day during weekends.
- Food Consumption, H_2O Intake, and Body Weights - 1x/week for Weeks 1-12 and 1x/4 weeks thereafter.
- ECG and Heart Rate (Lead I reading from ECG) - Weeks -1, 2, 16, 27, 55, and 76. (Pre-R, 2 and 4 hr post-dose. 5/sex from Groups 0 →3).
- Clinical Pathology - Hematology and Serum Chemistry: Weeks -2, 12, 25, 39, 52, 66, and 78; Urinalysis: Weeks 14, 25, 39(♂)/40(♀), 52(♂)/53(♀), 65, and 78; Fecal Occult Blood: Weeks -2, 2, 4, 11, 25, 39, 52, 53, 66, and 78 (5/sex/group from Week-2→52 and all animals thereafter). The following parameters were analyzed:

Hematology				
RBC	WBC and Differential	Reticulocyte	Hb	Ht
MCH	MCHC	MCV	TPT (Thromboplastin Time)	Platelets
Serum Chemistry				
ALT (SGPT)	Alkaline Phosphatase (ALP)	BUN	Glucose	
Leucine Arylamidase (Leucine Aminopeptidase) (LAP)		Glutamate Dehydrogenase	γ-Glutamyl Transpeptidase	
Sodium	Potassium	Calcium	Magnesium	
AST (SGOT)	Total Protein and Protein Fractions	Total Bilirubin	Total Cholesterol	
Creatinine	Chloride	Total Glycerol	Inorganic Phosphate	
Urinalysis and Fecal Occult Blood				
Specific Gravity, Color	pH	Glucose	Ketone Bodies	
Protein	RBC/Leukocyte	Nitrite	Urine Sediment Analysis	
Urobilinogen	Bilirubin	Urine Volume	Fecal Occult Blood	

- Ophthalmology (Ophthalmoscope & Slit Lamp) - Pre-R and Weeks 11, and 76.
- Necropsy - Week 79. The following organs from each group were preserved in [redacted] and examined microscopically (except femur and sternum). Tissues/organs with asterisk (*) were weighed. Bone marrow smears were prepared from each animals, but only smears from 5/sex animals in Groups 0 & 3 were evaluated.

Heart*	Lung*	Liver*	Kidneys*,1	Thymus*	Spleen*	Testes*,1
Adrenals*	Pituitary*	Thyroid with Parathyroids*		Brain* (Cerebrum & Cerebellum)		Prostate
Parotid Gland	Stomach	Duodenum	Jejunum	Ileum	Colon	Mesenteric Lymph Node
Aorta	Esophagus	Skeletal Muscle (Femoris)	Sublingual Gland	Submandibular Gland	Pancreas	Trachea
Epididymides	Uterus	Fallopian Tube	Ovaries*	Bladder	Skin	Mammary Glands
Lacrimal Gland	Sternum, Femur	Peripheral Nerve (Sciatic)[1]		Eye with Optic Nerve[1]	Lesions	Bone Marrow

* Tissues/Organs were weighed; [1] Tissues/Organs were fixed in Bouin's fluid.

- PK/TK - Months 14 (Group 1, 10/sex) and 18 (all animals from each group) at ~24 hr post dosing. Plasma UH-AC 62 XX levels were determined by a HPLC method.

Results:

- Clinical Signs and Mortality - A dose dependent increase in the mortality rate was noted. The incidence of unscheduled deaths or sacrificed at moribund for each group is summarized in the following table. Signs of anemia, wet bedding, intense urine odor, and blood-tinged urine were noted in the high dose group. The cause of one death in the control was not stated.

Group	Dose (mg/kg)	Found Dead		Sacrificed at Moribund	
0	0		1♀		
1	1.0	3♂		1♂	
2	2.0	2♂	4♀		
3	3.5	3♂	8♀	3♂	6♀

- Food Consumption, H_2O Intake, and Body Weights - Food consumption was not affected. Increased H_2O intake was noted in the mid- and high-dose ♀ (2.0 mg/kg: ↑17-34% during Weeks 24-78; 3.5 mg/kg: ↑13-99% during Weeks 8-78). Lower mean body weights were noted for all UH-AC 62 XX treated ♂ and mid- and high-dose ♀ and the % differences between the control and each treatment group are shown in the following table. The mean body weights taken immediately prior to necropsy were: ♂ - 687.7 g, 626.3 g (↓9%), 639.8 g (↓7%), and 583.7 g (↓15%) for 0, 2.0, and 3.5 mg/kg, respectively; ♀ - 356.6 g, 359.0 g, 327.9 g (↓8%), and 282.4 g (↓21%) for for 0, 2.0, and 3.5 mg/kg, respectively.

Group	Dose (mg/kg)	Mean Body Weight	
		♂	♀
1	1.0	↓6-9% (Wk 40→78)	-
2	2.0	↓6-7% (Wk 52→78)	↓6-7% (Wk 68→78)
3	3.5	↓6-14% (Wk 32→78)	↓7-18% (Wk 40→78)

- ECG and Heart Rate - No treatment-related changes were observed.
- Clinical Pathology -

Hematology: Alterations in hemograms and leukograms were secondary response to the GI injury caused by treatment with UH-AC 62 XX. These changes included:

- ↓ RBC: 3.5 mg/kg - ♀: ↓12-19%, Weeks 25→78;
- ↓ Ht: 3.5 mg/kg - ♂: ↓9-11%, Weeks 39→78; ♀: ↓10-15%, Weeks 25→78;
- ↓ Hb: 3.5 mg/kg - ♂: ↓7-10%, Weeks 52→78; ♀: ↓12-20%, Weeks 25→78;
- ↑ Reticulocyte: 3.5 mg/kg - ♂: ↑27-107%, Weeks 39→78; ♀: ↑54-241%, Weeks 25→78;
  2.0 mg/kg - ♂: ↑10-45%, Weeks 39→78;
- ↑ WBC: 3.5 mg/kg - ♂: ↑29-83%, Weeks 39→78; ♀: ↑26-227%, Weeks 25→78;
  2.0 mg/kg - ♂: ↑21-39%, Weeks 52→78; ♀: ↑23-79%, Weeks 39→78;
- ↑ PMN (Seg.): 3.5 mg/kg - ♂: ↑2.0-7.1x, Weeks 25→78; ♀: ↑1.3-13.0x, Weeks 12→78;
  2.0 mg/kg - ♂: ↑1.7-2.9x, Weeks 52→78; ♀: 1.3-3.8x, Weeks 25→78;
  1.0 mg/kg - ♂: ↑1.2-1.5x, Weeks 66→78; ♀: 1.2-2.0x, Weeks 39→78.
- ↑ Lymphocyte: 2.0 mg/kg - ♂: ↑20%, Week 78.

Chemistry: There were some significant changes in examined serum chemistry parameters:

- ↓ Total Cholesterol: 3.5 mg/kg - ♂: ↓20-31%, Weeks 66→78; ♀: ↓14%, Week 66;
  2.0 mg/kg - ♂: ↓14-15%, Weeks 66→78; ♀: ↓17-13%, Weeks 66→78;
  1.0 mg/kg - ♂: ↓15-18%, Weeks 66→78;
- ↓ Total Glycerol: 3.5 mg/kg - ♂: ↓24-60%, Weeks 12→78; ♀: ↓35-50%, Weeks 12 and 52→78;
  2.0 mg/kg - ♂: ↓7-16%%, Weeks 25→78; ♀: ↓12-26%, Weeks 12→78;
  1.0 mg/kg - ♂: ↓14-25%%, Weeks 12→78; ↓8-17%, Week 12, 52→66;
- ↓ Total Protein: 3.5 mg/kg - ♂: ↓8-12%, Weeks 39→78; ♀: ↓8-15%, Week 25→78;
  2.0 mg/kg - ♂: ↓6-7%, Weeks 52→66; ♀: ↓7-13%, Weeks 52→78;
- ↓ Albumin: 3.5 mg/kg - ♂: ↓8-28%, Weeks 12→78; ♀: ↓17-40%%, Weeks 25→78;
  2.0 mg/kg - ♀: ↓17-13%, Weeks 66→78;
  1.0 mg/kg - ♀: ↓9%, Week 78.

Urinalysis: Blood-tinged (reddish brown) urine was observed in UH-AC 62 XX treated ♀ with the incidence of:

- 3.5 mg/kg - 9 @ Week 25, 8 @ Week 39, 5 @ Week 52, and 3 @ Week 65;
- 2.0 mg/kg - 1 @ Week 25, 2 @ Weeks 39, 52, and 65;
- 1.0 mg/kg - 1 @ Weeks 65 and 78.

Fecal Occult Blood Test: Positive occult stool blood test was seen in 1♀ @ 2 and 2♀ @ 3.5 mg/kg at Week 52; 1♂+1♀ @ 0, 1♀ @ 2 and 2♂ @ 3.5 mg/kg. No positive test results were obtained during Weeks 68 and 78 analyses.

Bone Marrow Smear: Examinations of bone marrow smears from control and 3.5 mg/kg groups (5/sex) revealed that some significantly differences in the differential counts were identified in ♂ @ 3.5 mg/kg: ↑ myeloblastic, promyelocytic, myelocytic, neutrophils (↑26%); ↓ metamyeloblastic band neutrophils (↓15%); ↑ eosinocytes (↑95%); and ↑ plasma cells (44%).

- Ophthalmology (Ophthalmoscope & Slit Lamp) - No treatment-related changes were observed.
- Necropsy -

Organ Weights: A summary of major changes in absolute and relative organ weights is presented in the following table. The absolute weights of liver and thyroid decreased with the decrease of body weight.

Organ	1 mg/kg/day				2 mg/kg/day				3.5 mg/kg/day			
	Absolute Wt		Relative Wt		Absolute Wt		Relative Wt		Absolute Wt		Relative Wt	
	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Adrenal	↓14%	↑11%		↑10%	↓9%			↑13%	↓9%	↑10%		↑39%
Brain			↑5%				↑7%	↑5%			↑15%	↑21%
Heart		↑9%		↑8%	↓7%			↑11%	↓7%	↑16%	↑9%	↑47%
Kidneys		↓15%	↑5%	↑15%		↓9%	↑5%	↑19%		↓9%	↑11%	↑37%
Liver	↓9%				↓11%	↓13%			↓17%	↓15%		↑8%
Lung			↑7%				↑8%				↑12%	↑27%
Ovary		↓9%				↓16%		-		↓23%		
Pituitary	↓18%	↓25%		↓48%		↓31%		↓21%	↓19%	↓27%		↓16%
Prostate	↑20%		↑32%				↑7%		↑23%		↑44%	
Spleen	↓17%	↑6%	↓11%	↑6%	↓18%	↓13%		↑12%	↑12%	↑30%	↑33%	↑61%
Testes											↑16%	
Thymus		↑360%	↑29%	↑330%		↑17%	↑25%	↑32%		↑21%	↑16%	↑50%
Thyroid	↓18%	↓12%			↓6%	↓15%			↓11%	↓18%	↑6%	

Gross Pathology: Erosions of gastric mucosa and/or gastric ulcers were identified in 3♂ @ 1 mg/kg, 9♂ + 13♀ @ 2 mg/kg and 17 ♂ + 18♀ @ 3.5 mg/kg.

Histopathology: GI lesions of ulcers, erosion, scars and inflammatory changes were seen in 3♂+1♀ @ 1 mg/kg, 10♂+11♀ @ 2 mg/kg and 21♂+20♀ @ 3.5 mg/kg. In addition, chronic renal alterations with lesions of papillary necrosis and/or pyelonephritis were characterized in 1♀ @ 1 mg/kg, 6♀ @ 2 mg/kg and 2♂+19♀ @ 3.5 mg/kg.

- PK/TK - The mean plasma trough UH-AC 62 XX levels are shown in the following table.

Month	Mean Plasma UH-AC 62 XX Levels (μg/ml)*					
	1 mg/kg		2 mg/kg		3.5 mg/kg	
	♂	♀	♂	♀	♂	♀
14	9.8 (N=10)	19 (N=10)	-	-	-	-
18	16 (N=20)	17 (N=24)	23 (N=22)	21 (N=20)	32 (N=18)	32 (N=10)

* High inter-individual coefficient variations (CV) were observed with ranges of 32-57%.

Note:

1. **"Tube" was indicated as one of the organ parts preserved in [redacted] (Vol. 2.15, p 33 and Vol. 2.19, p 33). In the 4th amendment submission (dated August 19, 199), "fallopian tubes" and "Testes/ovaries with tubes" were included in the organ and tissue samples preserved in 10% formalin (Vol. 1, p 19). What does the term "tube" represent? The sponsor needs to provide an explanation for this particular organ.**
2. **The unit of reticulocyte count was stated as "0/00 of the erythrocytes" in the report (Vol. 2.15, p 27) and again it appeared in the 4th amendment submission (dated August 19, 199, Vol. 1, p 15). What does this unit "0/00" represent? Generally, the unit for reticulocyte count is expressed as % or N° of reticulocytes/1000 cells. An explanation from the sponsor is needed.**

2.2.2.7. U90-0408 Information on a preliminary toxicological study with UH-AC 62 XX in rats after intravenous administration. (Vol. 2.021, p 405)

U90-0409 Report on the histological investigation of organs from the preliminary investigation with the substance UH-AC 62 XX, study no. 99 N in rats. (Vol. 2.021. p 423)

Study N°: 99 N

Report Nº: U90-0408 and U90-0409 (Histopathology)
Study Aims: To determine the toxicity of UH-AC 62 XX following iv administration to rats for 4 weeks.
Compound: [redacted]
Vehicle Control: [redacted]
Dose and Route: [redacted]
Dosing Duration: 4-week
Animal: Rats, [redacted] (SPF), 65 (♂) & 89 (♀) days old, weighing 180-200 g, 5/sex/group.
Study Site: [redacted]
Dosing Date: 3/1/1988 - 3/14/1988
GLP/QAC Compliance: Not indicated.
Study Design:

Group	Compound	Dose (mg/kg)	Dose Vol. (ml/kg)	Dosing Duration	Nº of Animals	
					Toxicology	PK
0	Vehicle Control	0	8.0	4-week	5/sex	2/sex
1	UH-AC 62 XX	1.0	1.0		5/sex	2/sex
2		2.0	2.0		5/sex	2/sex
3		4.0	4.0		5/sex	2/sex
4		6.0	6.0		5/sex	2/sex
5		8.0	8.0		5/sex	2/sex

The following parameters were monitored.

- Clinical Signs and Mortality - 2x/day during Mondays → Fridays and 1x/week during weekends.
- Food Consumption, H_2O Intake, and Body Weights - 1x/week.
- Clinical Pathology - Hematology and Fecal Occult Blood: Weeks 1, 2, and 5; Serum Chemistry: Weeks 2 and 5; and Urinalysis: Weeks 2 and 4. The following parameters were analyzed:

Hematology				
RBC	WBC and Differential	Reticulocyte	Hb	Ht
MCH	MCHC	MCV	TPT and pTT	Platelets

Serum Chemistry					
ALT (SGPT)	Alkaline Phosphatase (ALP)		Aldolase	Glucose	BUN
Leucine Arylamidase (Leucine Aminopeptidase) (LAP)			Glutamate Dehydrogenase	γ-Glutamyl Transpeptidase	
Choline Esterase	Creatinine	Potassium	Calcium	Chloride	Inorganic Phosphate
AST (SGOT)	Total Protein	Protein Fractions	Total Bilirubin	Sodium	Magnesium

Urinalysis and Fecal Occult Blood				
Status (??)	Epithelial Excretion	NAG (N-acetyl-β-D-glucosaminidase) Excretion	Protein Excretion	Fecal Occult Blood

- PK/TK - Blood samples were taken prior to dosing on Days 2, 4, 7, 9, and 11. On day 14, blood was drawn at 0, 0.5, 1, 2, 4, 8, and 24 hr post dosing.
- Necropsy - Day 15. The following organs from each group were preserved in [redacted] and examined microscopically: liver, kidneys, stomach, samll and large intestines.

Results:

- Clinical Signs and Mortality - One ♂ @ 6 mg/kg died on Day 14. Rats @ 8 mg/kg were sacrificed during Week 1 of the study due to poor general health condition. **However, the actual date of sacrifice was not stated in the report.** Signs of anemia, lethargy, loss of appetite, reduced H_2O uptake, and deep breathing were observed in the rats @ ≥4 mg/kg/day.
- Food Consumption, H_2O Intake, and Body Weights - **Statement of slightly reduced body weight with ↓ food and H_2O consumption in rats @ 6 mg/kg was reported; however, no data were presented.**
- Clinical Pathology -

Hematology and Chemistry: Rats @ ≥4 mg/kg/day showed a ↓ in RBC, Hb, and Ht, an ↑ in MCV, reticulocyte count, and WBC with ↑ PMN; a ↓ in ALP, LAP, choline esterase, albumin, and total protein. A moderate increase in creatinine and BUN were also identified in ♀ @ ≥4 mg/kg/day. No **individual data were presented; therefore, the extent of ↑ or ↓ can not be evaluated by the reviewer.**

Urinalysis: Urinalysis was not performed in the high-dose group. Data showed that significantly ↑ epithelial excretion in ♂ (16.5x of control) & ♀ (6.1x) @ 6 mg/kg, ↑ NAG excretion in ♀ (2.6x) @ 4 mg/kg and 6 mg/kg, and ↑ protein excretion in ♀ (15.2x) @ 6 mg/kg during Week 4 analysis.

Fecal Analysis: Fecal occult blood test showed that increased incidence and intensity in (+) occult blood were noted in rats @ ≥4 mg/kg. **No actual data were submitted.**

- PK/TK - Data were illustrated in the graphic format. **But, the depicted graphs were not legible.**
- Necropsy - The major pathological aterations were found in the GI with lesions of erosions and ulcers/perforations in the stomach, ileum, and/or cecum) and kidneys with lesions of pyelonephritis and papillary necrosis. Dose-dependent GI injury was noted. The incidence of treatment-related pathological findings is presented in the following table.

Findings		1 mg/kg	2 mg/kg	4 mg/kg	6 mg/kg	8 mg/kg
Stomach	Erosions	1♀	4♂ + 5♀	3♂ + 4♀	2♂ + 2♀	No data Presented.
	Ulcers		1♂	2♂ + 3♀	4♂ + 5♀	
Ileum	Ulcers				1♂ + 1♀	
Cecum	Ulcers, chronic			3♀	2♀	
Kidneys	Pyelonephritis and/or Papillary Necrosis			1♂ + ♀		

Note: The report was poorly written and is incomprehensible. Actual data from several analyses were not presented. Graphs for plasma drug levels were not legible.

2.2.2.8. U89-0184 Subacute toxicity study of the substance UH-AC 62 XX in the rat following intravenous administration over a period of 4 weeks. (Vol. 2.022, p 1)

Study Nº: 13 O
Report Nº: U89-0184
Study Aims: To determine the toxicity of UH-AC 62 XX following iv administration to rats for 4 weeks with a 8-week recovery phase.
Compound:
Vehicle Control:
Dose and Route:
Dosing Duration: 4-week
Animal: Rats, [redacted] (SPF), 47 (♂) & 57 (♀) days old, weighing 200-250 g, 10-20/sex/group.
Study Site:
Study Date: 4/26/1988 - 8/8/1988
GLP/QAC Compliance: Yes
Study Design:

Group	Compound	Dose (mg/kg)	Dose Vol. (ml/kg)	Dosing Duration	Nº of Animals	
					Toxicology	PK
0	Vehicle Control	0	4.0	4-week	20/sex*	3/sex
1	UH-AC 62 XX	0.2	2.0		10/sex	3/sex
2		0.4	4.0		10/sex	3/sex
3		0.8	2.0		10/sex	3/sex
4		1.6	4.0		20/sex*	3/sex

* 10/sex from Groups 0 and 4 were allowed to have a 8-week recovery phase after the last dosing.

The following parameters were monitored.

- Clinical Signs and Mortality - 2x/day during Mondays → Fridays and 1x/week during weekends.
- Food Consumption, H_2O Intake, and Body Weights - 1x/week.
- Ophthalmoscopy - Pre-R, Weeks 4 and 13 (recovery phase).
- Heart Rate and ECG - Weeks -2, 1, 4, and 11; 5/sex from Groups 0, 3, and 4.
- Clinical Pathology - Weeks -2, 4, and 12 (recovery phase); Urinalysis: Weeks 4 and 12; and Fecal Occult Blood: Weeks -2, 1, 2, 4, and 11. The following parameters were analyzed:

Hematology					
RBC	WBC and Differential	Reticulocyte	Hb		Ht
MCH	MCHC	MCV	TT		Platelets
Serum Chemistry					
ALT (SGPT)	Alkaline Phosphatase (ALP)	Aldolase	Glucose		BUN
Leucine Arylamidase (Leucine Aminopeptidase) (LAP)		Total Glycerol	Total Cholesterol	γ-Glutamyl Transpeptidase	
Choline Esterase	Creatinine	Potassium	Calcium	Chloride	Inorganic Phosphate
AST (SGOT)	Total Protein	Protein Fractions	Total Bilirubin	Sodium	Magnesium
Urinalysis and Fecal Occult Blood					
Specific Gravity, Color	pH	Glucose	Ketone		
Protein	RBC/Leukocyte	Nitrite	Urine Sediment Analysis		
Urobilinogen	Bilirubin	Urine Volume	Fecal Occult Blood		
Epithelial Excretion	NAG (N-acetyl-β-D-glucosaminidase) Excretion		Protein Excretion		

- PK/TK - Blood samples were taken prior to daily dosing on Days 8, 14, 21, 28 and 29 immediately prior to necropsy.
- Necropsy - Weeks 4 and 12 (recovery phase).
  The following organs from each group were preserved in [redacted] and examined microscopically (except femur and sternum). Tissues/organs with asterisk (*) were weighed. Bone marrow smears were prepared from each animals, but only smears from 5/sex animals in Groups 0 & 4 were evaluated.

Heart*	Lung*	Liver*	Kidneys*,1	Thymus*	Spleen*	Bladder
Adrenals*	Pituitary*	Thyroid with Parathyroids*		Brain* (Cerebrum & Cerebellum)		Skin
Stomach	Small Intestine (Duodenum, Jejunum, Ileum)		Large Intestine (Colon, Cecum, Rectum)			Mesenteric Lymph Node
Testes*,♂	Prostate*	Epididymis	Cervical Lymph Node	Esophagus	Tongue	Injection Site
Aorta	Skeletal Muscle (Femoris)	Parotid Gland	Sublingual Gland	Submandibular Gland	Pancreas	Trachea
Uterus	Fallopian Tube	Ovaries	Mammary Glands		Spinal Cord[1]	
Lacrimal Gland	Sternum, Femur	Peripheral Nerve (Sciatic)[1]		Eye with Optic Nerve[1]	Lesions	Bone Marrow

* Tissues/Organs were weighed; [1] Tissues/Organs were fixed in [redacted]

Results:

- Clinical Signs and Mortality - There were no treatment-caused changes in behavior or clinical signs. One ♂ @ 0.4 mg/kg died under anesthesia prior to necropsy.
- Food Consumption, H_2O Intake, and Body Weights - There were no test article-induced effects on food consumption and body weight development. A slight but not statistical significant increase in H_2O intake was observed in the high-dose group during Week 4 and recovery phase (♂: ↑~9%, ♀: ↑~15%).
- Ophthalmoscopy - No-treatment related alterations were identified.
- Heart Rate and ECG - No apparent changes in heart rate and ECG caused by the treatment of UH-AC 62 XX were recorded.
- Clinical Pathology - No effects on hemogram, leukogram, coagulation, and serum chemistry parameters were noted. High-dose ♂ had slightly elevated NAG excretion value (↑27%) during Week 4 but not Week 12 (recovery phase). Positive occult blood tests were identified in 2♂ @ 1.6 mg/kg during Week 4.

- PK/TK - Female rats had higher plasma UH-AC 62 XX concentrations (2-5x) than ♂, an indicative of gender differences in drug metabolism. Mean plasma UH-AC 62 XX levels (μg/ml) of each group on Days 8, 14, 21, 28 and 29 (immediately prior to necropsy) are shown in the following table.

Day	0.2 mg/kg		0.4 mg/kg		0.8 mg/kg		1.6 mg/kg	
	♂	♀	♂	♀	♂	♀	♂	♀
8	0.76	2.34	2.22	7.35	2.76	9.55	5.42	26.71
14	0.63	3.25	2.47	7.85	2.72	12.59	3.54	28.66
21	0.95	2.83	3.64	7.48	2.79	10.67	6.82	29.27
28	1.07	2.92	3.01	8.12	4.24	10.7	7.59	32.00
29	1.30	3.59	3.80	9.07	4.21	13.14	6.05	32.60

- Necropsy -
  Organ Weights: There were some changes in absolute organ weights as shown in the following table.

Dose	Kidney		Spleen		Adrenal		Pituitary		Thyroid		Lung		Ovary
(mg/kg)	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♂	♀	♀
0.2					↑12%		↑30	↑13%	↑11%	↑11%			
0.4				↑10%	↑9%		↑14%	↑7%		↑12%		↑5%	↑10%
0.8				↑16%			↑11%	↑7%	↑7%	↑21%		↑13%	
1.6	↑7%		↑12%	↑10%	↑8%	↓12%	↑21%	↑8%	↑9%	↑9%		↑7%	
1.6*	↑11%	↓8%		↑15%	↑5%	↓9%	↑7%	↓10%					↑9%

* Recovery Phase

Gross and Histopathology: No gross lesions could be characterized at necropsy. The major microscopic changes were identified in the stomach (erosions and ulcer) and kidney (pyelonephritis). The incidence of these findings is shown in the below table.

Findings		0 mg/kg	0.2 mg/kg	0.4 mg/kg	0.8 mg/kg	1.6 mg/kg
Stomach	Erosions			2♂		3♂ + 2♀
	Ulcers					4♂ + 1♀
Kidneys	Pyelonephritis	1♀				4♂

Note: In the present report, microscopic gastric ulcer was only found in the animals @ 1.6 mg/kg. However, conflicting results were summarized by the sponsor. In the overall summary section, the sponsor stated that one ♂ @ 0.8 mg/kg had a gastric ulcer (Vol. 2.05, p 153). A clarification is needed from the sponsor.

2.2.3. *PIG STUDIES*

2.2.3.1. U81-0059 Toxicity study on the substance UH-AC 62 XX with oral administration to minipigs for 13 weeks. (Vol. 2.024, p 1)

U81-0058 Comparison of pharmacokinetic profiles of non-pretreated and subacutely pretreated minipigs. (Vol. 2.024, p 185)

Study N°: 20 G/80
Report N°: U81-0059 and U81-0058 (PK)
Study Aims: To determine oral toxicity of UH-AC 62 XX following administration to pigs for 13 weeks with a 6-week recovery phase.
Compound:
Dose and Route:
Vehicle Control:
Animal: minipigs, 3-4 months of age, weighing 9.2-14.5 kg, 3-6/sex/group.

Study Site: [redacted]
Study Date: 5/26/1980 - 11/2/1980
GLP/QAC Compliance: Not stated.
Study Design: Groups of pigs were randomly assigned to 4 groups and were orally dosed with either vehicle control or UH-AC 62 XX for 13 weeks as shown in the following table.

Group	Compound	Dose (mg/kg)	Dosing Duration	N°/Group
0	Strawberry Jam	0	13-week	3/sex
1	UH-AC 62 XX	1.0		3/sex
2		3.5		3/sex
3		10.0		6/sex*

* 3/sex were allowed to have a 6-week recovery phase after the last dose.

The following Parameters were conducted.

- Physical Examination (Body Temperature and Simple Motor Reflex Test) - Pre-R, Weeks 6, 13, and 19.
- Body Weights - 1x/week.
- Food Intakes - 1x/day.
- Clincal Pathology - Hematology and Clinical Chemistry, Weeks -1, 2, 6, 13, and 19; Urinalysis, Weeks 14 and 20. The following parameters were analyzed.

HEMATOLOGY		CHEMISTRY			URINALYSES
RBC	Platelet	AST (GOT)	Total Glycerol	Total Protein	Color/Turbidity
Reticulocyte	WBC and	ALT (GPT)	Lactase	Protein Fractions	pH
ESR	Differential	AP	Total Bilirubin	Calcium	Protein
MCH	Hb	LAP	Glucose	Sodium	Glucose
MCV	MCHC	GLDH	Cholesterol	Potassium	Ketone Bodies
Fibrinogen	Hematocrit (Ht)	CHE-S	Chloride	Inorganic Phosphate	Bilirubin
pTT	TPT	γGT	Magnesium		Nitrite
TT	Fibrin	BUN	Creatinine		Sediment Microscopic Examination

ESR = Erythrocyte Sedimentation Rate; pTT = Partial Thromboplastin Time; TPT = Thromboplastin Time; TT =Thrombin Time; AP = Alkaline Phosphatase; LAP = Leucine Aminopeptidase; GLDH = Glutamate Dehydrogenase; CHE-S = Choline Esterase; γGT = γ-Glutamyl Transferase.

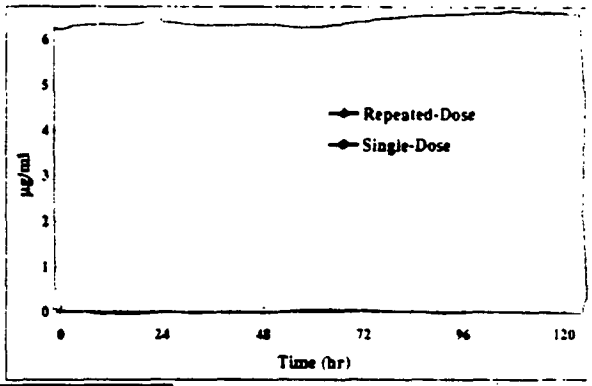
- PK/TK - Week 13. At the end of 13 weeks, a sigle oral dose of 3.5 mg/kg of [^{14}C]UH-AC 62 XX was given to 2/sex from Group 2 and 2/sex pigs (weighed 12.0-5.4 kg) that had never been treated previously serves as single-dose controls. Blood was drawn at 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 24, 30, 48, 72, 96, and 120 hr post dose for plasma drug level and metabolic pattern determination. Feces and urine were collected at 0-24, 24-48, 48-72, 72-96, and 96-120 hr post dose and radioactivity was determined.
- Necropsy - Weeks 14 and 20 (Recovery Phase) -
  Organ Weights: The following organs were determined at autopsy: heart and atrioventricular valves, brain, lung, pituitary, liver, thyroid, spleen, ovaries, kidneys, testes, adrenals, and prostate.
  Histopathology: The following organs/tissues were preserved in [redacted] and for the organs/tissues denoted with * were fixed in [redacted]

Heart and Atrioventricular Valves		Thymus	Tongue	Spinal Cord*
Aorta		Kidney*	Esophagus	Pituitary*
Lung	Trachea	Urinary Bladder	Stomach*	Peripheral Nerve (Sciatic Nerve)
Liver	Thyroid*	Adrenals*	Eye with Optic Nerve*	Skeletal Muscle (Biceps Femoris)
Gall Bladder		Pancreas*	Small Intestine*	Testes*
Spleen		Submandibular Gland	Large Intestine*	Epididymides
Lymph Nodes (Cervical, Intestinal)		Bone Marrow	Brain* (Cortex, Thalamus, Hypothalamus,	Seminal Vesicle
Uterus		Ovary*	Cerebellum Medulla Oblongata)	Prostate

Sections of the above listed organs/tissues except bone marrow from all animals were examined microscopically. To detect neutral fats and lipids, frozen sections of the myocardium, liver, kidneys and adrenals were stained with fat red 7 B.

Results:

- Mortality and Clinical Signs - No deaths occurred. No remarkable changes were identified.
- Body Weights and Food Intakes - Comparable data were obtained for UH-AC 62 XX treated pigs and controls.
- Clincal Pathology - No treatment-related anomalies in all analyzed parameters were noted.
- Gross- and Histo-Pathology - No significant changes in organ weights were identified. Gastric ulcers were identified in 1♀ @ 3.5 mg/kg and 1♂ @ 10 mg/kg during gross examination and were confirmed with microscopic examination. In addition to gastric ulcers, lesions of purulent bronchopneumonia were noted in 1♂ and 1♀ @ 3.5 mg/kg.
- PK/TK - UH-AC 62 XX was absorbed and systemically available. Plasma concentrations of UH-AC 62 XX at various time points following administration of [^{14}C]UH-AC 62 XX are depicted in the right figure. The mean (±SE) AUC values for single and 13-week repeated dosing were 56.90 ± 5.05 and 117.42 ± 17.99 μg•hr/ml, respectively. Higher plasma peak and AUC values were observed in the repeated dosing group, an indicative of accumulation. Cumulative % radioactive dose excreted in urine and feces is listed in the following table.



Time (hr)	% Radioactive Dose					
	Single-Dose			Repeated-Dose		
	Urine	Feces	Total	Urine	Feces	Total
0-24	40.0	1.6	43.5	14.9	2.7	19.0
0-48	44.2	29.6	76.3	43.6	32.5	77.9
0-72	44.9	44.5	90.9	50.6	46.1	95.5
0-96	45.1	48.2	93.4	51.3	48.1	98.8
0-120	45.3	48.4	93.9	51.7	49.3	100.3

- Plasma Metabolic Pattern - **The presented TLC migration diagram was blurry and uninterpretable.**

2.2.3.2. U87-0199 Chronic toxicity study on the substance UH-AC 62 XX with oral administration to minipigs for 52 weeks. (Vol. 2.025, p 1)

U93-0472 Toxicokinetic monitoring of UH-AC 62 XX in minipigs at the middle dose of a long term toxicity study (52 weeks) at daily oral doses of 1, 3 and 9 mg/kg (study N° 54 L). (Vol. 2.026, p 229)

Study N°: 54 L

Report Nº: U87-0199/U93-0472 (PK)
Study Aims: To assess the spectrum of adverse effects of UH-AC 62 XX with long-term daily oral administration in minipigs for 52 weeks.
Compound:
Dose and Route:
Vehicle Control:
Dosing Duration: 52 Weeks
Animal: , 10-12 months of age, weighing 8.6-13.0 kg for ♂ and 8.0-11.6 kg for ♀, 4/sex/group.
Study Site:
Study Date: 9/25/1984 - 10/9/1985
GLP/QAC Compliance: Yes
Study Design: Minipigs were randomly assigned to 4 dose groups and given UH-AC 62 XX at 0, 1, 3.0, or 9 mg/kg/day in gelatin capsules by oral gavage for 52 weeks as shown in the following table.

Group	Treatment	Dose (mg/kg/day)	Dosing Duration	Nº of Animals
G 0	Empty Capsules	0	52-Week	4/sex
G 1	UH-AC 62 XX	1.0		
G 2		3.0		
G 3		9.0		

The following observations were conducted:

- Clinical Signs and Mortality - 2x/day.
- Body Weights - 1x/week.
- Food Intakes - 1x/week.
- ECG (Leads I, II and III) and Heart Rate - Weeks -1, 2, 6, 14, 28, and 49; 4/sex from Groups 0, 2, and 3, Pre-R and 2 hr post dosing.
- Clincal Pathology (Hematology, Clinical Chemistry and Urinalysis) - Weeks -1, 2, 7, 13/14, 28, 39, and 52 for all animals. The following parameters were analyzed.

HEMATOLOGY			CHEMISTRY					URINALYSES	
RBC		Platelet	AST (GOT)		HBDH		Total Protein	Color/Turbidity	
Reticulocyte		WBC and	ALT (GPT)		Aldolase	CK	Protein Fractions	pH	Glucose
ESR		Differential	AP	GT	Inorganic Phosphate		BUN / Creatinine	Ketone Bodies	
MCH		Hb	LAP	LDH	Total Bilirubin		Phospholipids	Protein	
MCV		MCHC	GLDH	CHE-S	Glucose		Uric Acid	Bilirubin	
Fibrinogen	Fibrin	Hematocrit (Ht)	Lactate		Cholesterol		Sodium / Calcium	Nitrite	
pTT	TT	TPT	Triglycerides		Chloride	Magnesium	Potassium	Sediment Examination	

- Fecal Occult Blood - Days 2, 3, and 4 of Weeks -2, 1, 3, 6, 12, 25, 38, and 51.
- Toxicokinetics - Blood samples were collected from 4 (2/sex) Group 2 (3.0 mg/kg) animals at 0, 2, 4, and 6 hr after dosing on Day 1 and at Weeks 28 and 52.
- Necropsies - Week 52. The following organs were weighed and organ to body weight ratios were calculated: heart, lung, liver, spleen, kidneys, adrenals, brain, pituitary, thyroids, ovaries, prostate, and testes.
  The following tissues from each animal were preserved in formalin or in (tissues with *). Sections from these tissues were examined microscopically.

Heart	Kidneys*	Submandibular Gland								Skeletal Muscle (Biceps)			
Aorta	Urinary Bladder	Tongue								Bone Marrow (Sternum, Femur)			
Lung	Pituitary Gland*	Esophagus								Skin			
Trachea	Thyroids*	Stomach (Cardia, Fundus, Pylorus)								Testes	Prostate		
Liver	Pancreas*	Duodenum*	Jejunum*	Ileum*						Epididymides	Seminal Vesicle		
Gallbladder	Adrenal Glands*	Eye + Optic Nerve*								Ovaries*	Uterus		
Lymph Nodes (Jejunal, Popliteal, Cervical)		Cecum*	Rectum*	Colon*						Vagina	Mammary Gland		
Brain* (Cerebrum, Cerebellum, Cortex,	Spinal cord (Cervical, Thoracic, Lumbar)									Thymus			
Thalamus, Hypothalamus, Medulla)	Sciatic Nerve	Spleen								Gross Lesions			

Bone marrow smears were prepared for all animals. Only the smears from control and high-dose groups were examined. Frozen sections of the myocardium, liver, kidneys and adrenals were stained with oil red 7 B to detect neutral fats and lipids.

Results:

- Mortality and Clinical Signs - A total of 5 unscheduled deaths (2♀ @ 1.0 mg/kg on Days 10/11 and 269/270; 1♀ @ 3.0 mg/kg sacrificed at moribund; 2♂ @ 9.0 mg/kg on Days 160/161 and 335/336). Lethargy, listless, hypothermia, ataxia, and loss of appetite were major observations in these pigs prior to death.
- ECG and Heart Rate - No drug-related effects were recorded.
- Food Consumption and Body Weights - Reduced food consumption with lower body weight in the pigs that died or were sacrificed during the study as stated by the sponsor. **Individual data are illegible; therefore, evaluations of the body weight changes can not be performed.**
- Hematology and Clinical Chemistry - **Due to small sample sizes, marked individual variations, and no consistent changes noted in the same individuas, a conclusion of observed changes in hematograms, leukograms, serum chemistry and urinalysis attributable to the treatment can not be made.**
- Fecal Occult Blood Test - Positive test results were noted in one Group 1 ♀ (Nº 151) that died of perforated esophagus on Day 10/11 and 1 Group 3 ♂ prior to death.
- Pathology -

  Organ Weights: There were some changes in absolute lung, liver, spleen, kidney, adrenal, thyroid and testes weight in ♂ and kidney, ovary, adrenal, and thyroid weight in ♀ as shown in the following table.

Dose	Adrenal		Kidney		Thyroid		Lung	Liver	Spleen		Testes	Ovaries
mg/kg	♂	♀	♂	♀	♂	♀	♂	♂	♂	♀	♂	♀
1	↑33%	↑11%		↑10%	↑27%	↑9%	↑25%	↑22%			↑50%	↓13%
3	↑24%	↓13%	↑8%	↑12%	↑26%	↓5%	↑51%	↑25%	↑25%	↑6%	↑68%	↓6%
9	↑24%	↓18%	↑2%	↑16%	↑40%	↑66%	↑53%	↑36%	↑34%	↑7%	↑43%	↑11%

  Gross Pathology: Gastric ulcer (~4 cm in diameter) was found in only one high-dose ♀ pig. Acute→chronic bronchopneumonia was seen in 2 @ 0 mg/kg, 6 @ 1 mg/kg, 5 @ 3 mg/kg and 3 @ 9 mg/kg.

  Microscopic Pathology: Lesions of chronic gastric healed ulceration and scarring were identified in 1♀ @ 9 mg/kg and 1♂ @ 3 mg/kg, respectively.
- Toxicokinetics - The individual plasma concentration data as well as mean calculated AUC_{0-6} values are summarized in the following table. The C_{max} at steady state were 0.8-3.1 μg/ml and 1.7-4.3 μg/ml at Weeks 28 and 52 respectively. Based on presented results, accumulation occurred after repeated dosing. In addition, a gender-difference in the drug metabolism was observed as mean C_{max} and AUC values were 1.5-3.0x higher in ♂ as compared to ♀. This observation was inconsistent with the data obtained from another study (2.2.3.3, Study Report Nº U92-0253).

Sampling Day / Sampling Time (hr)		Plasma UH-AC 62 XX (µg/ml)			
		♂ Pig Nº		♀ Pig Nº	
		201	202	251	252
Day 1	0.0	BQL	BQL	BQL	BQL
	2.0	0.64	0.50	0.35	0.29
	4.0	1.67	1.98	1.15	0.78
	6.0	NE	1.05	0.62	0.56
	AUC_{0-6} (µg•hr/ml)	-	5.91	3.57	2.69
Week 28	0.0	0.19	0.36	0.26	0.13
	2.0	1.68	1.28	0.53	0.81
	4.0	3.11	1.84	0.62	0.60
	6.0	3.00	1.59	0.77	0.72
	AUC_{0-6} (µg•hr/ml)	12.77	8.18	(3.33)*	3.66
Week 52	0.0	0.29	0.49	0.39	0.17
	2.0	4.34	0.93	0.63	2.72
	4.0	3.75	1.96	2.05	1.71
	6.0	2.31	1.46	1.88	0.95
	AUC_{0-6} (µg•hr/ml)	18.65	7.71	7.63	9.83

Estimation, using the linear trapezoidal rule; BQL = Below Quantitation Limit

Note: **Individual data for the body weight changes are illegible; therefore, evaluation of the body weight changes can not be performed. No summary tables for clinical laboratory findings were provided. A lot of specimens from various tissue/organs showed "autolysis" in the reports of microscopic findings, an indicative of poor sample collections.**

2.2.3.3. U92-0253 Toxicity study on UH-AC 62 XX in minipigs by oral application over a period of 12 months. Toxicokinetics of UH-AC 62 XX during chronic toxicity study (12 months) of UH-AC 62 XX in minipigs following oral administration. (Vol. 2.026, p 246 - Vol. 28, p. 259)

Study Nº: 09 O/B32 (PK).
Report Nº: U92-0253
Study Aims: To assess the spectrum of adverse effects of UH-AC 62 XX with long-term daily oral administration in minipigs for 52 weeks with a 13-week recovery phase.
Compound:
Dose and Route:
Vehicle Control:
Dosing Duration: 52 Weeks
Animal: , 5-6 months of age, weighing 6.4-11.2 kg for ♂ and 7.6-14.3 kg for ♀, 6/sex/group.
Study Site:
Dosing Date: 10/19/1988 -10/17/1989
Recovery Phase: 101/18/1989 - 1/16/1990
GLP/QAC Compliance: Yes
Study Design: Minipigs were randomly assigned to 4 dose groups and given UH-AC 62 XX at 0, 1, 2.5 or 6 mg/kg/day in gelatin capsules by oral gavage for 52 weeks as shown in the following table. Recovery animals, 2/sex/group, were kept without treatment for an additional 13 weeks.

Group	Treatment	Dose (mg/kg/day)	Dosing Duration	Nº of Animals
G 0	Empty Capsules	0	52-week with a 13-week recovery phase	6/sex*
G 1	UH-AC 62 XX	1.0		
G 2		2.5		
G 3		6.0		

* 2/sex from each group were allowed to have a 13-week recovery phase.

The following observations were conducted:

- Clinical Signs and Mortality - 1x/day.
- Body Weights - 1x/week.
- Food Intakes - 1x/week.
- Ophthalmoscopy - Pre-R and weeks 8, 13, 26, 41, 52 and 65 (recovery).
- Electrocardiography (Leads I, II and III) and Heart Rate - Pretest and Weeks 2, 6, 14, 28, 50 and 65 (recovery), Pre-R and 2 hr post dosing.
- Clincal Pathology - Hematology and Clinical Chemistry, Pre-R and Weeks 1, 7, 13, 26, 39, 52 and 65 (recovery) for all animals; Urinalysis, Pre-R and Weeks 8, 13, 26, 39, 52 and 65 (recovery) and at necropsy. The following parameters were analyzed.

HEMATOLOGY			CHEMISTRY					URINALYSES	
RBC	Platelet		AST (GOT)	HBDH		Total Protein		Color/Turbidity	
Reticulocyte	WBC and		ALT (GPT)	Aldolase	CK	Protein Fractions		pH	Glucose
ESR	Differential		AP	γGT	Inorganic Phosphate	BUN	Creatinine	Ketone Bodies	
MCH	Hb		LAP	LDH	Total Bilirubin	Phospholipids		Protein	
MCV	MCHC		GLDH		Glucose	Uric Acid		Bilirubin	
Fibrinogen	Hematocrit (Ht)		CHE-S		Cholesterol	Sodium	Calcium	Nitrite	
pTT	TT	Thromboplastin Time	Triglycerides		Chloride Magnesium	Potassium		Sediment Microscopic Examination	

- Fecal Occult Blood - Pre-R and Weeks 1, 6, 12, 25, 38, 51 and 64 (recovery).
- Toxicokinetics - Blood samples were collected from the first 4 animals (2/sex) in each drug treated group at 0, 2, 4, 5 and 24 hours after dosing on Day 1 and at Weeks 25 and 52.
- Necropsies - Weeks 52 (4/sex/group) and 65 (2/sex/group, recovery). The following organs were weighed and organ to body weight ratios were calculated: heart, thymus, ovaries, lung, pancreas, prostate, liver, brain, seminal vesicles, spleen, pituitary, uterus, kidneys, thyroids, salivary glands, adrenals, and testes.

  The following tissues from each animal were preserved in formalin (testes, eyes and one kidney from each animal were preserved in [redacted]).

Heart + Atrioventricular Valves	Kidneys	Salivary Glands	Skeletal Muscle (Biceps)	
Aorta	Urinary bladder	Tongue	Bone Marrow (Sternum, Femur)	
Lung	Pituitary gland	Esophagus Larynx	Skin	
Trachea	Thyroids	Stomach (Cardia, Fundus, Pylorus)	Testes	Prostate
Liver	Pancreas	Duodenum Jejunum Ileum	Epididymides	Seminal Vesicle
Gallbladder	Adrenal Glands	Eye + Optic Nerve	Ovaries	Uterus
Lymph Nodes (Jejunal, Popliteal, Cervical)		Cecum Rectum Colon	Vagina	Mammary Gland
Brain (Cerebrum, Cerebellum)	Spinal cord (Cervical, Thoracic, Lumbar)		Thymus	
Parotid Gland	Sciatic Nerve	Spleen	Gross Lesions	

Sternum bone marrow smears were prepared for all animals. Only the smears from control and high-dose groups (4/sex) were examined.

Results:

- Mortality and Clinical Signs - No deaths occurred. Signs of emesis were noted in all groups including the control sporadically. Three high-dose animals had emesis more frequently in later course of study, two of them had emesis almost daily during the last two-thirds of the study.
- ECG and Heart Rate - No drug-related effects were recorded.
- Food Consumption and Body Weights - No treatment-related effects observed.
- Hematology and Clinical Chemistry- No treatment-related effects were observed.
- Fecal Occult Blood Test - Fecal occult blood was not detected.
- Pathology -

Organ Weights: Slightly higher absolute and relative liver and adrenal weights, as shown in the following table, without confirming histopathological changes were observed in the high-dose ♂.

Dose (mg/kg)	Absolute Organ Weight (g)		Relative Organ Weight	
	Liver	Adrenal gland	Liver	Adrenal gland
Control	303	1.8	16.9	0.103
1.0	326	2.1	17.4	0.112
2.5	317	2.1	18.2	0.119
6.0	383* (↑26%)	2.4* (↑33%)	22.3* (↑32%)	0.137* (↑33%)

* significant $p \leq 0.05$

Gross Pathology: No treatment-related changes detected.
Microscopic Pathology: No treatment-related histopathological changes detected.

- Toxicokinetics - A linear relationship between dose and plasma drug levels was noted. No gender diferences in AUC and C_{max} values were observed. Mean PK/TK parameters of UH-AC 62 XX on Day 1, and in Weeks 25 and 52 are given in the following table.

Dose (mg/kg/day)	C_{max} (µg/ml)			AUC_{0-24} (µg•hr/ml)		
	Day 1	Week 25	Week 52	Day 1	Week 25	Week 52
1.0	0.480	0.722	0.518	5.065	7.878	6.710
2.5	1.398	1.040	0.868	13.015	12.232	12.982
6.0	3.165	3.220	2.092	35.818	42.792	30.150

Base on the presented data, MTD was not achieved.

2.2.3.4. U82-0080 Toxicity study on the substance UH-AC 62 XX with intravenous administration to minipigs for 5 weeks. (Vol. 2.028, p 317)

Study Nº: 41 H/82
Report Nº: U82-0080
Study Aims: To assess the spectrum of adverse effects of UH-AC 62 XX following iv administration to minipigs for 5 weeks.
Compound: [redacted]
Dose and Route: [redacted]
Vehicle Control: [redacted]
Dosing Duration: 5 Weeks
Animal: [redacted] minipigs, 7-9 months of age, weighing 9-15.7 kg, 3/sex/group.
Study Site: [redacted]
Study Date: 2/1/1982 - 5/3/1982
GLP/QAC Compliance: Yes
Study Design: Minipigs were randomly assigned to 4 dose groups and given UH-AC 62 XX at 0, 1, 3.0 or 9.0 mg/kg/day by iv for 5 weeks as shown in the following table. Animals, 3/sex from Group 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	Empty Capsules	0	0.675	5-week	3/sex
G 1	UH-AC 62 XX	1.0	0.075		3/sex
G 2		3.0	0.225		3/sex
G 3		9.0	0.675		6/sex*

* 3 sex from each group were allowed to have a 6-week recovery phase.

The following Parameters were conducted.

- Clinical Signs and Mortality - 1x/day.

- Physical Examination (Body Temperature, Hearing Function, and Simple Motor Reflex Test) - Pre-R, Weeks 5 and 11.
- Body Weights - 1x/week.
- Food Intakes - 1x/day.
- Heart Rate and ECG (Lead I, II, and III) - Weeks -1, 2, 5 and 11 (recovery phase); Groups 0, 2, and 3, 3/sex.
- Ophthalmoscopic Examination - Pre-R, Weeks 4 and 10.
- Clincal Pathology - Hematology and clinical chemistry, Weeks -1, 5, and 11; Urinalysis, Weeks 5, and 11. The following parameters were analyzed.

HEMATOLOGY		CHEMISTRY			URINALYSES	
RBC	Platelet	AST (GOT)	Total Glycerol	Total Protein	Color/Turbidity/Sp. Gr.	
Reticulocyte	WBC and	ALT (GPT)	Total Bilirubin	Protein Fractions	pH	
ESR	Differential	AP	BUN	Calcium	Protein	Blood
MCH	Hb	LAP	Glucose	Sodium	Glucose	
MCV	MCHC	GLDH	Cholesterol	Magnesium	Ketone Bodies	Nitrite
Fibrinogen	Hematocrit (Ht)	CHE-S	Chloride	Potassium	Bilirubin	Urobilinogen
pTT Fibrn	TPT	γGT	Creatinine	Inorganic Phosphate	Sediment Microscopic Examination	

- PK/TK - **Not determined.**
- Necropsy - Weeks 5 and 11 (Recovery Phase) -
  Organ Weights: The following organs were determined at autopsy: heart, brain, lung, pituitary, liver, thyroid, spleen, ovaries, kidneys, testes, adrenals, and prostate.
  Histopathology: The following organs/tissues were preserved in [redacted] and for the organs/tissues denoted with * were fixed [redacted]

Heart	Thymus	Tongue	Spinal Cord *
Aorta	Kidney*	Esophagus	Pituitary*
Lung	Urinary Bladder	Stomach* (Cardia, Fundus, Pylorus)	Peripheral Nerve (Sciatic Nerve)
Trachea	Thyroid w/ Parathyroids*	Mammary Gland	Eye with Optic Nerve*
Liver	Adrenals*	Jugular Vein (Injection Site)	Skeletal Muscle (Biceps Femoris)
Gall Bladder	Pancreas*	Small Intestine* (Duodenum, Jejunum, Ileum)	Testes*
Bone Marrow (Sternum)	Submandibular Gland	Large Intestine* (Colon, Cecum, Rectum)	Epididymides
Spleen	Sublingual Gland	Brain* (Cortex, Thalamus, Hypothalamus,	Seminal Vesicle
Ovary Oviduct	Parotid Gland	Cerebellum Medulla Oblongata)	Prostate
Skin	Uterus	Lymph Nodes (Jejunal, Popliteal, Cervical)	Gross Lesions

Sections of the above listed organs/tissues except bone marrow from all animals were examined microscopically. To detect neutral fats and lipids, frozen sections of the myocardium, liver, kidneys and adrenals were stained with fat red 7 B.

Results:

- Clinical Signs and Mortality - No deaths occurred. No remarkable clinical signs were noted.
- Body Weights and Food Consumption - Comparable mean body weights were noted between control and treated pigs.
- Heart Rate, ECG, and Ophthalmocopic Examination - No significant changes attributable to the treatment were observed.
- Clinical Pathology - There were no differences in group mean values for all of analyzed hematology, serum chamistry and urinalysis parameters. One each ♀ in Groups 2 and 3 had slightly lower values for Hb (↓16 and ↓29%, respectively) and RBC (↓21 and 32%, respectively) at Week 5. One Group 3 ♀ had elevated γGT (2x) during Week 5.
- Gross and Histopathology - Ulcers (~1 cm diameter, 2♀ @ 9 mg/kg), purulent bronchopneumonia (1♀ @ 9 mg/kg), and abscess in the injection site (1♂ @ 1.0 and 1♂ and 1♀ @ 9.0 mg/kg) (an

indicative of poor injection technique) were noted during gross examination. Microscopic examination revealed ulcers in 2♀ @ 9 mg/kg and healed ulcers in one recovery ♀.

2.2.3.5. U92-0310 UH-AC 62 XX: Repeated dose toxicity study in micro-pigs by intravenous administration over a period of 4 weeks. (Vol. 2.029, p 1)

Toxicokinetics of UH-AC 62 XX during 4 weeks toxicity study of UH-AC 62 XX in micro pigs following intravenous administration. (Vol. 2.029, p 49)

Study Nº: 68 Q and B 39 (PK)
Report Nº: U92-0310
Study Aims: To determine toxicity of UH-AC 62 XX following iv administration to pigs for 4 weeks.
Compound:
Dose and Route:
Vehicle Control:

Animal: 30 micropigs, 17-21 months of age, weighing 15.5-25.8 kg, 3-6/sex/group.
Study Site:
Study Date: 6/17/1991 (1st dosing) - 8/25/1991
GLP/QAC Compliance: Yes
Study Design: Groups of pigs were randomly assigned to 4 groups and were dosed with either vehicle control or UH-AC 62 XX for 4 weeks by iv injection as shown in the following table.

Group	Compound	Dose (mg/kg)	Dosing Vol. (ml /kg)	Dosing Duration	Nº/Group
0	Placebo	0	0.675	13-week	3/sex
1	UH-AC 62 XX	1	0.1		3/sex
2		3	0.3		3/sex
3		9	0.675		6/sex*

* 3/sex were allowed to have a 6-week recovery phase after the last dose.

The following Parameters were conducted.

- Clinical Signs and Mortality - 2x/day.
- Physical Examination (Body Temperature, Hearing Function, and Simple Motor Reflex Test) - Pre-R, Weeks 4 and 10.
- Body Weights - 1x/week.
- Food Intakes - 1x/day.
- Heart Rate and ECG (Lead I, II, and III) - Weeks -2, 4 and 9; Groups 0, 2, and 3, 3/sex.
- Ophthalmoscopic Examination - Pre-R, Weeks 4 and 10.

- Clincal Pathology - Hematology and clinical chemistry, Weeks -1, 4, and 10; Urinalysis, Weeks -2, 4, and 10. The following parameters were analyzed.

HEMATOLOGY		CHEMISTRY				URINALYSES	
RBC	Platelet	AST (GOT)	Total Glycerol	Total Protein		Color/Turbidity	
Reticulocyte	WBC and Differential	ALT (GPT)	Lactase	Protein Fractions		pH	
ESR		AP	Total Bilirubin	Calcium	Sodium	Protein	Blood
MCH	Hb	LAP	BUN	Magnesium		Glucose	
MCV	MCHC	GLDH	Glucose	Potassium		Ketone Bodies	Nitrite
Fibrinogen	Hematocrit (Ht)	CHE-S	Cholesterol	Inorganic Phosphate		Bilirubin	Urobilinogen
pTT	TT	TPT	γGT	Chloride	Creatinine	Sediment Microscopic Examination	

- PK/TK - Blood samples were taken on Days 1, 3, 7, 14, 21, and 28 prior to the daily dosing for the determination of drug trough levels by an HPLC method.
- Necropsy - Weeks 4 and 10 (Recovery Phase) -
  Organ Weights: The following organs were determined at autopsy: heart, brain, lung, pituitary, liver, thyroid, spleen, ovaries, kidneys, testes, adrenals, and prostate.
  Histopathology: The following organs/tissues were preserved in [redacted] and for the organs/tissues denoted with * were fixed [redacted]

Heart	Lung	Kidney*	Bone Marrow (Sternum, Femur)	Spinal Cord (neck, Chest, Loin)
Aorta	Trachea	Urinary Bladder	Stomach (Cardia, Fundus, Pylorus)	Pituitary
Liver	Gall Bladder	Mandibular Gland	Mammary Gland	Peripheral Nerve (Sciatic Nerve)
Thyroid	Adrenals	Sublingual Gland	Area of Injection	Eye with Optic Nerve*
Ovary	Uterus	Parotid Gland	Small Intestine (Duodenum, Jejunum, Ileum)	Skeletal Muscle (Biceps Femoris)
Tongue	Esophagus	Prostate Testes*	Large Intestine (Colon, Cecum, Rectum)	Lymph Nodes (Jejunal, Popliteal, Cervical)
Pancreas	Thymus	Seminal Vesicle	Brain (Cortex, Thalamus, Hypothalamus, Cerebellum Medulla Oblongata)	Gross Lesions
Spleen	Skin	Epididymides		

Sections of the above listed organs/tissues except bone marrow from all animals were examined microscopically. To detect neutral fats and lipids, frozen sections of the myocardium, liver, kidneys and adrenals were stained with fat red 7 B.

Results:

- Clinical Signs and Mortality - One ♂ @ 9 mg/kg expired on Day 61/62 (recovery phase) with signs of sedation and decreased food intake prior to death.
- Body Weights and Food Consumption - Comparable mean body weights were noted between control and treated pigs. Only 1♂ @ 9 mg/kg had decreased food intake (↓51%) during Week 8 (recovery phase).
- Heart Rate, ECG, and Ophthalmocopic Examination - No significant changes atributable to the treatment were observed.
- Clinical Pathology - No treatment-related changes in any of analyzed hematology, serum chemistry and urinalysis parameters. No positive findings in fecal occult blood were identified.
- Gross and Histopathology - No treatment-related lesions were noted. Pulmonary thrombosis with cardiac failure was characterized in the ♂ @ 9 mg/kg that died on Day 61/62.
- PK/TK - Mean (±SD) plasma UH-AC 62 XX levels (ng/ml) on Days 3, 7, 14, 21, and 28 for each dose group are listed in the following table.

Sampling Day	1 mg/kg/day		3 mg/kg/day		9 mg/kg/day	
	♂	♀	♂	♀	♂	♀
3	12.20 ± 1.27	15.60 ± 0.92	44.10 ± 6.51	55.40 ± 25.15	135.17 ± 123.48	254.37 ± 148.12
7	10.10	13.33 ± 3.44	28.97 ± 8.75	69.53 ± 56.22	95.97 ± 80.18	98.70 ± 22.91
14	12.05 ± 0.07	22.27 ± 14.34	34.23 ± 27.49	42.83 ± 9.45	91.67 ± 94.30	171.50 ± 165.30
21	12.35 ± 0.78	14.20 ± 4.40	28.60 ± 3.69	79.23 ± 68.69	101.63 ± 52.04	232.33 ± 187.66
28	12.50 ± 0.85	16.30 ± 0.62	46.35 ± 17.99	67.5 ± 67.89	322.80 ± 139.30	74.60 ± 40.75

Based on the presented results, no adverse toxicity was noted for all measured parameters; therefore, **MTD was not achieved in the current study.**

2.2.4. DOG STUDIES

2.2.4.1. U85-0018 Oral tolerability of UH-AC 62 XX in dogs. (Vol. 2.031, p 1)

U90-0621 Plasma level monitoring during an oral tolerance study of UH-AC 62 XX in dogs (Vol. 2.052, p 1)

Study Nº: 26 L
Report Nº: U85-0018 and U90-0621 (Plasma levels)
Study Aims: To determine the highest dose of UH-AC 62 XX that would not cause any GI toxicity following 3-week oral administration to dogs.
Compound:
Formulation:
Dose and Route:
Dosing Duration: 3-week
Animal: beagle dogs, 12-13 months of age, weighing 12.6-15 kg for ♂ and 8.9-13.2 kg for ♀, 1/sex/group.
Study Site:
Study Date: 5/7/84 - 7/9/84
GLP/QAC Compliance: Yes
Study Design: Groups of 1/sex beagle dogs were orally given with UH-AC 62 XX in gelatin capsule for 3 weeks at doses listed in the below table.

Group	Compound	Dose (mg/kg)	Dosing Vol. (ml /kg)	Dosing Duration	Nº/Group
1	UH-AC 62 XX	1.2	0.09	3-week	1/sex
2		0.6	0.045		
3		0.4	0.03		

The following observations were conducted:

- Clinical Signs and General Behavior - 1x/day.
- Food Consumption and Body Weights - Pre-R, 1x/week.
- Stool Occult Blood Test - Days 2,3, 4, 9, 10, 11, 16, 17. and 18.
- Blood Drug Levels - Days 1, 3, and 5 of each week.
- Necropsy - Day 22. GI from each animal was preserved for histopathological examination.

Results:

- Clinical Signs and Mortality - The Group 1 ♀ died on Day 8 as a result of GI toxicity (perforated gastric ulcer). Vomiting and apathetic were general clinical symptoms observed in this high-dose ♀. The ♂ in Group 1 was sacrificed on Day 8.
- Food Consumption and Body Weights - The average food consumption and body weight changes for each dog during the study are presented in the following table. Both high-dose ♂ and ♀ and mid-dose ♀ had reduced body weights, measured at the time of necropsy, and ↓ food consumption.

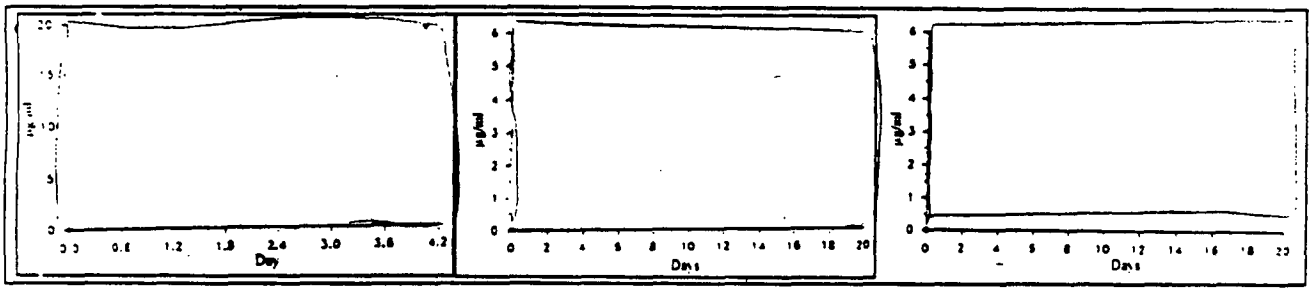
Dog ID	Sex	Dose	Food Consumption (g) Study Week					Body Weight (kg) Study Week					At
		(mg/kg)	-2	-1	1	2	3	-2	-1	1	2	3	Necropsy
101	♂	1.2	249	279	259	-	-	12.6	12.4	12.1			11.5
151	♀	1.2	330	326	89	-	-	13.2	13.0	12.9			12.0
401	♂	0.6			400	400	400			15.0	15.2	15.0	15.0
451	♀	0.6			294	162	186			9.3	9.4	9.2	8.7
501	♂	0.4			400	400	400			13.0	13.0	12.9	13.0
551	♀	0.4			182	241	251			8.9	8.8	9.0	9.0

- Stool Occult Blood Test - The results of fecal occult blood test are shown in the following table.

Dog ID	Dose (mg/kg)	Study Day 2	3	4	9	10	11	16	17	18
101	1.2	0	2	2						
151	1.2	0	2	2						
401	0.6	0	ND	0	2	2	2	0	0	1
451	0.6	1	1	1	2	2	2	1	1	2
501	0.4	0	0	1	1	1	0	1	1	0
551	0.4	0	1	2	1	2	2	1	1	2

ND = Not Determine; 0 = Negative; 1 = Slight +; 2 = Marked +

- PK/TK - Data showed that UH-AC 62 XX was absorbed and systemically available in all dose groups following oral administration. Plasma UH-AC 62 XX levels for each dog during the course of study are depicted in the following three figures.



- Necropsy - The major gross pathological changes in each dogs are as following:

ID N°	Sex	Dose (mg/kg)	Necropsy Gross Findings
101	♂	1.2	pyloric ulcers (2-15 mm in diameter), reddish small intestinal mucosa
151	♀	1.2	pyloric ulcers (up to 2 cm in diameter)/perforation/erosions, grayish-brown fetid abdominal fluid (250 ml).
401	♂	0.6	pyloric ulcers (~2 mm in diameter)/erosions.
451	♀	0.6	Not remarkable.
501	♂	0.4	Not remarkable.
551	♀	0.4	Not remarkable.

Gastric ulcers were identified in all high- and mid-dose groups during microscopic examinations.

2.2.4.2. U92-0788 UH-AC 62 XX (meloxicam): 4-week oral tolerance study in dogs. (Vol. 2.031, p 24)

Study Nº: H50
Report Nº: U92-0788
Study Aims: To determine the tolerance and possible undesirable side effects of UH-AC 62 XX following 4-week oral administration to dogs.
Compound:
Vehicle Control:
Dose and Route:
Dosing Duration: 4-week
Animal: 24 beagle dogs, 10-20 months of age, weighing 7-12 kg, 3/sex/group.
Study Site: Boehringer Ingelheim KG, D-6507 Ingelheim, Germany.
Study Date: 3/30/1992 - 4/27-28/1992
GLP/QAC Compliance: Yes
Study Design: Groups of 3/sex beagle dogs were orally given with UH-AC 62 XX by gavage for 4 weeks at doses listed in the below table.

Group	Compound	Dose (mg/kg)	Dosing Vol. (ml /kg)	Dosing Duration	Nº/Group
0	UH-AC 62 XX	0	0.27	4-week	3/sex
1		0.1	0.07		
2		0.2	0.013		
3		0.4	0.27		

The following observations were conducted:

- Clinical Signs and General Behavior - >1x/day.
- Food Consumption - 1x/day.
- Body Weights - Pre-R, 1x/week.
- Stool Occult Blood Test - Weeks -1, 1, 2, 3, and 4.
- ECG, Body Temperature - Weeks -1, 2, and 4, at 2 and 24 hr post dose.
- Clinical Pathology (Hematology, Blood Chemistry & Urinalysis) - Weeks -1, 2, and 4.
- Necropsy - Day 28/29.
  Organ Weights: The following listed organs were weighed: heart, lung, liver, kidneys, adrenals, thyroid glands, spleen, brain, gonads, prostate, pituitary, and mandibular salivary glands.
  Histopathology: The following tissues were preserved in solution and processed for microscopic examination: stomach, duodenum, jejunum, ileum, cecum, colon, rectum, kidneys, and macroscopic lesions.
- Blood Drug Levels - Not monitored.

Results:

- Clinical Signs and Mortality - No observed clinical signs are treatment-related.
- Food Consumption and Body Weights - No significant differences between UH-AC 62 XX treated and control dogs were observed.
- Stool Occult Blood Test - Results were inconclusive as positive tests were noted in the control dogs too.
- ECG and Body Temperature - No remarkable changes attributable to the treatment were recorded.
- Clinical Pathology - No treatment-related changes were seen.
- Necropsy - No pathological alterations were noted.

No adverse effects on all monitored parameters were observed; therefore, **MTD was not achieved in the current study.**

2.3. CARCINOGENICITY STUDIES

2.3.1. *MOUSE STUDY*

2.3.1.1. U91-0333 Long-term feeding study of UH-AC 62 XX in mice. 07 January 1991. (Vol. 2.032-2.034)

U92-0404 Toxicokinetic monitoring in the 4 mg/kg dose group during a long term feeding study of UH-AC 62 XX in mice (protocol no. 4184/87). (Vol. 2.034, p 329)

U92-0663 UH-AC 62 XX: Histological examination of mice joints. (Vol. 2.034, p 349)

Study Nº: 4184/87
Report Nº: U91-0333, U92-0404 (PK/TK), and U92-0663
Study Aims: To determine the carcinogenic potential of UH-AC 62 XX following oral administration via diet admix to mice for ≥99 weeks.
Compound:
Dose and Route:
Animal: mice, 25-27 days of age, weighing 14-18 g, 100/sex/group for control and 50/sex/group for UH-AC 62 XX treated groups.
Study Site:
Study Date: 8/11/1987 - 8/9/1989
GLP/QAC Compliance: Yes
Study Design: Groups of 50-100/sex mice were randomly assigned to four groups and received diet containing 0, 2, 4, and 8 mg/kg/day of UH-AC 62 XX. Additional 20/sex were assigned to 4 mg/kg/day group for the PK/TK study.

Group	Dose (mg/kg/day)	Route	Dosing Duration	Nº of Animals	
				Toxicology	PK/TK Study
1 (Control 1)	0	Oral via Diet Admix	♂: 104 Weeks ♀: 99 Weeks	50/sex	-
2 (Control 2)	0			50/sex	-
3	2			50/sex	-
4	4			50/sex	20/sex
5	8			51♂, 49♀	-

The following observations were conducted.

- Clinical Signs - 1x/day. Started from Week 27, all animals were examined for palpable masses 1x/week.
- Mortality - 2x/day.
- Food Consumption - 1x/week through Week 13 and 1x/2 weeks thereafter.
- H_2O Consumption - 1x/day.
- Body Weights - 1x/week through Week 13, 2x/week thereafter.
- Ophthalmic Examination and Inspection of Auditory Acuity and Dentition - Week 99(♀)/104 (♂).
- Hematology (RBC, WBC and Differential) - Weeks 52, 78, and the end of study.
- Test Article Bioavailability - Blood samples were collected at Weeks 1, 30, 60, 60, 99(♀)/104(♂) for plasma drug level determination via an HPLC method. The limit of quantitation was
- Necropsy - Unscheduled deaths and terminal sacrifices (Week 104). Due to poor survival, female mice were sacrificed during Week 99. The following listed tissues or representative samples were

collected and preserved in [redacted]. Tissues designated with a single asterisk were weighed. Paired organs were weighed together.

Aorta	Adrenals	Kidneys*	Skin	Prostate	Ovaries
Bone (Os Femoris)	Bone Marrow (Os Femoris)	Larynx	Lesions	Seminal Vesicle	Testicles
Brain*	Bronchi	Liver*	Lungs*	Salivary Gland	
Costo-Chondral Junction (Rib)		Pancreas	Pituitary	Spleen*	
Ear (Internal, External)		Lymph Nodes (Mesenteric and Mandibular)		Stomach	
Epididymides		Mammary Gland		Thymus	
Eyes (With Optic Nerve)		Mesovary		Thyroids (with Parathyroids)	
Gall Bladder		Muscle, Skeletal		Uterus (Cervix)	Vagina
Heart*		Nasal Cavity (And Pharynx)		Trachea	Tumors
Intestine, Large (Colon Rectum, Cecum)		Nerve, Sciatic	Spinal Cord	Urinary Bladder	
Intestine, Small (Duodenum, Jejunum, Ileum)		Esophagus		Tongue	

The following organs as shown in the table and gross lesions, tissue masses or suspect tumors, regional lymph nodes from all UH-AC 62 XX treated mice were subjected to histopathological examinations.

Respiratory System	Urinary System	Circulatory System
Lungs (with Mainstem Bronchi), Trachea	Kidneys, Urinary Bladder	Heart, Aorta
Integumentary System	**Hepatopancreatic System**	**Endocrine System**
Skin, Mammary Gland	Liver, Pancreas, Gall Bladder	Pituitary, Thyroids, Parathyroids, Adrenals
Hematopoietic/Lymphatic System	**Reproductive System**	**Nervous System**
Mesenteric Lymph Node, Mandibular Lymph Node, Spleen, Bone Marrow (Femur), Thymus	Testicles, Epididymides, Prostate, Seminal Vesicle, Ovaries, Mesovary, Uterus (Incl. Cervix), Vagina	Brain (3 Sections Incl. Frontal Cortex, Basal Ganglia, Parietal Cortex, Thalamus, Cerebellum, Pons), Spinal Cord, Sciatic Nerve
Sense Organ	**Digestive System**	**Musculoskeletal System**
Eyes With Optic Nerve, Ears (Internal and External), Nasal Cavity (Incl. Pharynx), Others, Larynx	Stomach, Intestine, Intestines (Small and Large), Esophagus, Salivary Gland, Tongue (Incl. Base)	Skeletal Muscle (Thigh), Bone (Femur), Costo-Chondral Junction (Rib)

Knee joints and hip joints (with parts of the pelvis) were prepared at final autopsy from 12 ♂/group.

Results:

- Clinical Signs and Mortality - No remarkable changes in clinical signs or behavior were attributable to treatment with UH-AC 62 XX. Female mice were sacrificed at Week 99 due to high mortality. Comparable survival rates were identified in all groups. The accumulated mortality for each group is listed in the following table.

Study Week	Mortality (%)							
	Control		2		3		4	
	♂	♀	♂	♀	♂	♀	♂	♀
Week 52	1/100 (1.0%)	9/100 (9.0%)	3/50 (6%)	4/50 (8%)	5/50 (10%)	1/50 (2%)	5/51 (9.8%)	2/49 (4.1%)
Week 78	18/100 (18%)	34/100 (34%)	9/50 (18%)	15/50 (30%)	14/50 (28%)	19/50 (38%)	11/51 (21.6%)	19/49 (38.8%)
Week 99	45/100 (45%)	75/100 (75%)	23/50 (46%)	38/50 (76%)	32/50 (0.64)	41/50 (82%)	27/51 (52.9%)	36/49 (73.5%)
Week 104	60/100 (60%)	-	27/50 (54%)	-	35/50 (70%)	-	32/51 (62.7)	-

- Food and H_2O Consumption - No treatment-associated changes in the food consumption were noted. However, some minor sporadic changes (either ↑ or ↓) were observed during the entire study period. The actual doses of UH-AC 62 XX consumed by each group are presented in the following table.

Dose		Control		2		3		4	
		♂	♀	♂	♀	♂	♀	♂	♀
Proposed Dose	Weeks 1-99 (♀)/104 (♂)	0	0	2.0	2.0	4.0	4.0	8.0	8.0
Actual Dose	Weeks 1-13	0	0	1.93	1.96	3.87	3.93	7.74	7.88
	Weeks 15-99 (♀)/104 (♂)	0	0	1.99	1.98	3.98	3.98	7.96	7.94

- Body Weights - There were no significant changes attributable to the treatment.
- Ophthalmic Examination and Inspection of Auditory Acuity and Dentition - No effects were recorded.
- Hematology - No significant changes were detected at Weeks 52, 78, and 99(♀)/104(♂).
- PK/TK - Blood samples were collected from PK satellite rats (4 mg/kg/day only) during Weeks 1, 30, 60, and 80. Mean (±SD) plasma trough levels of UH-AC 62 XX are shown in the following table.

Week	Mean (±SD) Plasma UH-AC 62 XX Levels (μg/ml)	
	♂ (N=20)	♀ (N=20)
1	0.157 ± 0.062[a]	0.146 ± 0.047[b]
30	0.542 ± 0.165	0.378 ± 0.169
60	0.561 ± 0.130	0.509 ± 0.174
80	0.450 ± 0.198	0.564 ± 0.319

[a] N=17; [b] N=6.

- Necropsy -

  Organ Weights: Increased absolute (28%, p≤0.05) and relative (38%) spleen weights were noted in high-dose ♂.

  Microscopic Examination of Joints: Sections of the hip, knee, and ankle joints (with the interphalangeal joints) from 12 ♂/group were evaluated. Degenerative changes of these joints were noted in most animals. The severity and incidence of these findings were comparable between UH-AC 62 XX treated animals and controls. Therefore, treatment with UH-AC 62 XX did not alter the severity and incidence of spontaneously occurring degenerative joint disorder in aged mice.

  Gross and Histopathology Non-neoplastic Findings: No treatment-related non-neoplastic lesions were identified.

  Gross and Histopathology Neoplastic Findings: Significant positive trend for hepatocellular adenoma and pituitary adenoma was noted by the sponsor in ♀ with p values of 0.0049 and 0.023, respectively using [redacted] (time-adjusted) as listed in the following table. However, the analysis performed by the agency's statistician showed that p values for hepatocellular adenoma and pituitary adenoma were 0.0148 and 0.4450, respectively using the exact permutation trend test. **Both hepatocellular adenoma and pituitary adenoma are common tumors based on concurrent controls or historical data provided by the sponsor; therefore, these statistical values might not implicate any biological significance.**

Tumor	Statistical Method	Tumor Incidence (N° of Animals w/ Tumors/N° of Animals Used)								Trend Test	
		Control		2.0 mg/kg/day		4.0 mg/kg/day		8.0 mg/kg/day			
		♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Hepatocellular Adenoma (Benign)		6/100	0/100	2/50	1/50	0/50	0/50	3/51	3/49	-	-
		-	-	p=0.4655	p=0.3334	p=0.0834	p=1.0000	p=0.6420	p=0.0342		
		6/100	0/100	2/50	1/50	0/50	0/50	3/51	3/49	p=0.5480	p=0.0234
		5/100	0/100	1/50	1/50	0/50	0/50	3/51	3/49[a]	p=0.4574	p=0.0049
Pituitary - Adenoma (Benign)		1/100	9/100	0/50	12/50	0/50	4/50	0/51	6/49	-	-
		-	-	p=0.6667	p=0.0141	p=0.6667	p=0.5521	p=0.6623	p=0.3627		
		1/100	9/100	0/50	12/50	0/50	4/50	0/51	6/49	p=0.3041	p=0.8648
		1/100	8/100	0/50	11/50[a]	0/50	4/50	0/51	6/49	p=0.8269	p=0.0230

[redacted] liver [redacted] context 1; [a] pituitary [redacted] context 1 and 2, [redacted] context 1 and 1 and 2 were combined for the statistical analysis, context 3 and 4 were excluded. Therefore, the number of animals with tumors given in this table in the row [redacted] test may be different from the number of animals with tumors in the rows [redacted] exact test and [redacted] test.

A summary of statistical analysis of specific tumor combined incidence in mice is presented in the following table. A significant p value of 0.039 was noted for hepatocellular adenoma + carcinoma by the [redacted] analysis method. But, it was not shown to be significant with the [redacted] time-adjust test as stated by the sponsor. A p value of 0.033 was obtained by the agency's statistician using the exact permutation trend test.

Organ Tumor Type	Dose (mg/kg/day)								Statistical Significance *Brandt-Snedecor p-value		
	Control I & II		4		6		8				
	♂	♀	♂	♀	♂	♀	♂	♀			
Skin/Mammary Gland - Papillomas + Squamous Cell Carcinomas		1/100		0/50		1/50		0/49	NS	♀	0.630
Skin - Adenocancroid + Carcinomas + Carcino-Sarcomas	1/100	4/100	0/50	2/50	0/50	1/50	1/51	2/49	NS	♂ ♀	0.634 0.925
Lung Adenomas + Carcinomas + Adenocarcinomas	22/100	12/100	8/50	9/50	11/50	7/50	9/51	2/49	NS	♂ ♀	0.791 0.186
All Tissues: Hemangiomas + Hemangiosarcomas	3/100	4/100	2/50	1/50	2/50	1/50	2/51	3/49	NS	♂ ♀	0.982 0.647
(Uterus/Uterine Region)		1/100		0/50		0/49		1/49			
(Skin)	0/100	1/100	0/50	0/50	0/50	0/50	0/51	1/49			
(Spleen)	1/100	0/100	0/50	0/50	0/50	0/50	0/51	0/49			
(Liver)	2/100	2/100	2/50	1/50	2/50	1/50	2/51	1/49			
Stomach (Fore) - Papillomas (Squamous Cell) + Carcinomas	0/100	1/100	0/50	0/50	0/50	1/50	0/51	0/49	NS	♂ ♀	0.791 0.630
Stomach (Glandular) + Intestine Adenomatous Polyps	1/100	1/100	0/50	0/50	0/50	0/50	0/51	1/49	NS	♂ ♀	0.687 0.619
Liver - Hepatocellular Adenomas + Carcinomas	7/100	0/100	2/50	2/50	0/50	0/50	3/51	3/49	NS a	♂ ♀	0.283 0.039
Adrenal Gland - Cortical Adenomas + Carcinomas	9/99	1/99	4/50	1/50	3/50	0/50	6/50	0/49	NS	♂ ♀	0.763 0.630
Uterus - Adenofibromas + Carcinomas		0/100		1/50		2/49		0/49	NS	♀	0.145
Sarcomas		2/100		3/50		2/49		3/49	NS	♀	0.549

NS = not significant, p>0.05; * (Chi-square) devised [redacted] a p< 0.05

No toxic effects on all monitored parameters (clinical signs, body weights, hematology, gross and histopathology); therefore, MTD was not achieved in the present study. At doses up to 8 mg/kg/day, UH-AC 62 XX did not cause significant differences in the incidence of all observed tumors in mice.

Note: No indication of radiolabeled compound was used for PK/TK study; however, presented structure showed that it was isotope labeled molecule (Vol. 2.034, p 335).

2.3.2. RAT STUDY

2.3.2.1. U92-0645 Long-term feeding study of UH-AC 62 XX in Sprague-Dawley rats. 15 June 1992. (Vol. 2.035-2.037)

U92-0405 Toxicokinetic monitoring in the 0.6 mg/kg dose group during a long term feeding study of UH-AC 62 XX in rats (protocol no. 3805/86) (Vol. 2.038, p 1)

U92-0490 Histological examination of rat joints. (Vol. 2.038, p 22)

Study Nº: 3058/86; B92 (TK)
Report Nº: U92-0645; U92-0405 (TK); U92-0490
Study Aims: To determine the carcinogenic potential of UH-AC 62 XX following oral administration via diet admix to rats for ≥104 weeks.
Compound:
Dose and Route:
Dosing Duration: 104 weeks
Animal: Sprague-Dawley rats 5-6 weeks of age, weighing 113-128.8 g, 50/sex for each UH-AC 62 XX treated group and 100/sex for control.
Study Site:
1st Dosing Date: 12/02/1986
Study Termination: 12/12/1988
GLP/QAC Compliance: Yes
Study Design: Groups of 50-100/sex rats were randomly assigned to four groups and received diet containing 0, 0.4, 0.6, and 0.8 mg/kg/day of UH-AC 62 XX. Additional 20/sex were assigned to 0.6 mg/kg group for the PK/TK study. The doses selected based on data obtained from a 18-month chronic toxicity showing that UH-AC 62 XX at 1.0 mg/kg caused deaths (3/24), gastric ulcer (2/24) and renal papillary necrosis (5/24).

Group	Dose (mg/kg/day)	Route	Dosing Duration	Nº of Animals	
				Toxicology	PK/TK Study
1 (Control 1)	0	Oral via Diet Admix	104 Weeks	50/sex	-
2 (Control 2)	0			50/sex	
3	0.4			50/sex	-
4	0.6			50/sex	20/sex
5	0.8			50/sex	-

The following observations were conducted.

- Clinical Signs - 1x/day. Started from Week 27, all animals were examined for palpable masses 1x/week.
- Mortality - 2x/day.
- Food Consumption and Body Weights - 1x/week through Week 13, 2x/week thereafter.
- Ophthalmic Examination and Inspection of Auditory Acuity and Dentition - Week 105/106.
- Hematology (RBC, WBC and Differential) - Weeks 52, 78, and 104.
- PK/TK - Blood samples were collected from the satellite group at Weeks 1, 30, 60, and 80 for the detemination of plasma drug level via an HPLC method. The limit of quantitation
- Necropsy - Unscheduled deaths and terminal sacrifices (Week 105/106). The following listed tissues or representative samples were collected and preserved in . Tissues designated with a single asterisk were weighed. Paired organs were weighed together.

Aorta	Kidneys*	Prostate
Adrenals*	Larynx	Salivary Gland
Bone (Os Femoris)	Liver*	Seminal Vesicle
Bone Marrow (Os Femoris)	Lungs* Lesions	Skin
Brain*	Lymph Nodes (Mesenteric and Mandibular)	Spinal Cord
Bronchi	Mammary Gland	Spleen*
Costo-Chondral Junction (Rib)	Mesovary/Mesometrium	Stomach
Ear (Internal, External)	Muscle, Skeletal	Thymus*
Epididymides	Nasal Cavity (and Pharynx)	Thyroids (with Parathyroids)*
Eyes (with Optic Nerve)	Nerve, Sciatic	Testicles*
Gall Bladder	Esophagus	Tongue
Heart*	Ovaries*	Trachea Tumors
Intestine, Large (Colon Rectum, Cecum)	Pancreas	Urinary Bladder
Intestine, Small (Duodenum, Jejunum, Ileum)	Pituitary*	Uterus (Cervix) Vagina

The following organs as shown in the table and gross lesions, tissue masses or suspect tumors, regional lymph nodes from all UH-AC 62 XX treated mice were subjected to histopathological examinations.

Respiratory System	Urinary System	Circulatory System
Lungs (with Mainstem Bronchi), Trachea	Kidneys, Urinary Bladder	Heart, Aorta
Integumentary System	**Hepatopancreatic System**	**Endocrine System**
Skin, Mammary Gland	Liver, Pancreas	Pituitary, Thyroids, Parathyroids, Adrenals
Hematopoietic/Lymphatic System	**Reproductive System**	**Nervous System**
Mesenteric Lymph Node, Mandibular Lymph Node, Spleen, Bone Marrow (Femur), Thymus	Testicles, Epididymides, Prostate, Seminal Vesicle, Ovaries, Mesovary, Uterus (Incl. Cervix), Vagina	Brain (3 Sections Incl. Frontal Cortex, Basal Ganglia, Parietal Cortex, Thalamus, Cerebellum, Pons), Spinal Cord, Sciatic Nerve
Sense Organ	**Digestive System**	**Musculoskeletal System**
Eyes With Optic Nerve, Ears (Internal and External), Nasal Cavity (Incl. Pharynx), Others, Larynx	Stomach, Intestine, Intestines (Small and Large), Esophagus, Salivary Gland, Tongue (Incl. Base)	Skeletal Muscle (Thigh), Bone (Femur), Costo-Chondral Junction (Rib)

Knee, hip and ankle joins were prepared at final autopsy from 39 @ 0, 22 @ 0.4, 15 @ 0.6, and 19 @ 0.8 mg/kg/day for histopathological evaluation.

Results:

- Clinical Signs and Mortality - No remarkable changes in clinical signs or behavior were attributable to the treatment with UH-AC 62 XX. Comparable survival rates were identified in all groups. The mortality for each group at the end of study is listed in the following table.

Study Week	Mortality (%)							
	Control 1+2		0.2 mg/kg		0.4 mg/kg		0.8 mg/kg	
	♂	♀	♂	♀	♂	♀	♂	♀
104	32% (32/100)	36% (36/100)	44 (22/50)	32% (16/50)	20% (10/50)	38% (19/50)	30% (15/50)	30% (15/50)

- Food Consumption and Body Weights - The actual intake of UH-AC 62 XX for each group is shown in the following table. High dose group animals had slightly increased food consumption during Weeks 1→70 (♂: ↑ up to 6%; ♀: ↑ up to 13%). There were no significant changes attributable to the treatment.

Proposed Dose (mg/kg/day)		0.4		0.6		0.8	
		♂	♀	♂	♀	♂	♀
Actual Dose (mg/kg/day)	Weeks 1-13	0.38 ± 0.02	0.38 ± 0.02	0.56 ± 0.03	0.58 ± 0.03	0.75 ± 0.03	0.77 ± 0.03
	Weeks 15-104	0.40 ± 0.01	0.40 ± 0.01	0.60 ± 0.02	0.59 ± 0.02	0.79 ± 0.03	0.79 ± 0.03

- Examinations of Eyes, Hearing and Dentition - No treatment-related effects were recorded.
- Hematology - Comparable results were noted between UH-AC 62 XX treated rats and controls at Weeks 52, 78 and 104.

- PK/TK - Blood samples were collected from PK satellite rats (0.6 mg/kg group only) during Weeks 1, 30, 60, and 80. Mean (±SD) plasma trough UH-AC 62 XX levels for both ♂ and ♀ are listed in the following table. Higher plasma UH-AC 62 XX concentrations were noted in ♀ rats at Weeks 1, 30, and 60.

Week	Mean (±SD) Plasma UH-AC 62 XX Levels (μg/ml)	
	♂ (n=20)	♀ (n=20)
1	2.98 ± 1.19	4.15 ± 1.73
30	6.65 ± 2.19	8.83 ± 3.30
60	6.96 ± 3.10	11.07 ± 3.84
80	9.14 ± 4.17	9.91 ± 3.95

- Necropsy -

  Organ Weights: No differences were recorded between treatment groups and controls.

  Macroscopic Findings: Multiple hemorrhagic foci were identified in the control and UH-AC 62 XX treated animals. No other distinct changes or exceptional tumors were noted in the UH-AC 62 XX treated groups.

  Histological Examination of Joints: Histological evaluations of joints (hip, knee and ankle) were performed on 39 @ 0, 22 @ 0.4, 15 @ 0.6, and 19 @ 0.8 mg/kg/day. Results showed that osteoarthrosis of ankle joint was seen in most of rats. The incidence of osteoarthritis in knee and hip joints was much less than that in the ankle joint. Treatment with UH-AC 62 XX did not change the spontaneous rate of osteoarthritis in rats.

  Microscopic Neoplastic Findings: Treatment with UH-AC 62 XX at doses 0.4, 0.6, and 0.8 mg/kg/day for 104 weeks did not cause increased incidence for all examined tumors in rats.

  Microscopic Non-neoplastic Findings: Significant non-neoplastic findings are listed in the following table. However, no significant GI lesions were characterized. The only other pathological changes attributable to the treatment were lesions of papillary necrosis and pyelonephritis. **Papillary necrosis and pyelonephritis are often recognized as toxic effects caused by long term treatment with NSAID and usually occurs at a higher incidence in the ♂ rats. The severity of islet cell hyperplasia was not addressed in the pathology report.** There were no differences in the severity of bile duct hyperplasia observed in the controls and UH-AC 62 XX treated animals.

Non-neoplastic Microscopic Findings		Control 1		Control 2		0.4 mg/kg		0.6 mg/kg		0.8 mg/kg	
		♂	♀	♂	♀	♂	♀	♂	♀	♂	♀
Cardiomyopathy (1+)		25	20	25	26	25	18	26	18	35[c]	29
Stomach	Erosions	4	7	5	6	10	5	7	12	8	7
	Peptic Ulcer	0	0	1	0	1	0	1	0	1	3
Liver - Bile Duct Hyperplasia (1+)		2	0	2	3	4	5[a]	7	6[a]	7[a]	7[b]
Pancreas - Islet Cell Hyperplasia		9	5	18[a]	16[b]	21[b]	13[a]	25[c]	29[d]	29[c]	26[c]
Kidney	Interstitial Nephritis	20	3	17	6	17	9	32[f]	14[d]	24	14[d]
	Papillary Necrosis (onset, calcified)	0	0	0	0	0	0	2	12[e]	1	23[e]
	Pyelonephritis (slight, sequestral) (1+→3+)	0	0	0	0	0	0	0	0	0	8[e]
Mammary Gland - Mastopathy (proliferating, cystic)		0	0	0	0	0	0	2	8[e]	1	1

[a] Significant different from control 1 (p≤0.05); [b] Significant different from control 1 (p≤0.01); [c] Significant different from control 1 + 2 (p≤0.05); [d] Significant different from control 1 (p≤0.01) + Significant different from control 2 (p≤0.05); [e] Significant different from control 1 (p≤0.01) + Significant different from control 2 (p≤0.01); [f] Significant different from control 1 (p≤0.05) + Significant different from control 2 (p≤0.01).

Note: No indication of radiolabeled compound was used for PK/TK study; however, presented structure showed that it was isotope labeled molecule (Vol. 2.038, p 10).

2.4. REPRODUCTIVE TOXICITY STUDIES

2.4.1. *FERTILITY AND PRENATAL (SEGMENT I)*

2.4.1.1. U91-0903 Reproduction studies with UH-AC 62 XX in rats dosed orally before mating and during early period of gestation. 30 April 1991. (Vol. 2.044, p 190)

Study Nº: 359-1328
Report Nº: U91-903
Study Aims: To determine the adverse effects of UH-AC 62 XX on the fertility of male and female rats and early embryonic development.
Compound:
Dose and Route:
Vehicle Control:
Dosing Period: ♂: 9-week prior to mating and throughout mating for a total of 12 weeks.
♀: 2-week prior to mating through Gestation Day (GD) 7
Animals: Sprague-Dawley Slc:SD rats, 6 weeks of age weighing 144.5-208.9 g for ♂ and 9 weeks of age weighing 160.7-206.3 g for ♀, 34/group.
Study Site:
Study Date: 6/27/1990 - 4/30/1991
GLP/QAC Compliance: Yes
Basis of Dose Selection: Results from a 13-week toxicity study and a 2-week pilot study for Segment I study (0, 3.5, 7 and 10 mg/kg/day) showed that maximum tolerable dose for ♀ was 3.5 mg/kg and 7.0 mg/kg for ♂. Therefore, 9 and 5 mg/kg were designated as the high-dose for ♂ and ♀, respectively.
Study Design: Male rats were orally dosed with 0, 1, 2.5 and 9 mg/kg/day of UH-AC 62 XX starting from 9 weeks (~6 weeks old) prior to mating and throughout mating for a total of 12 weeks. Female rats were orally given 0, 1, 2.5 and 5 mg/kg/day of UH-AC 62 XX from 2 weeks prior to mating through GD 7.

Group	Compound	Dosing Period		Dose (mg/kg)		Nº of Rats/Dose		Time of Rats Sacrificed	
		♂	♀	♂	♀	♂	♀	♂	♀
0	Vehicle Control	9-week prior to mating throughout mating	2-weeks prior to mating through GD 7	0	0	34	34	Week 12 (after mating)	GD 21
1	UH-AC 62 XX			1	1	34	34		
2				2.5	2.5	34	34		
3				9	5	34	34		

The following observations were conducted.

- Clinical Signs and Mortality - 2x/day.
- Body Weights - 1x/day during dosing period.
- Food and H_2O Consumption - 1x/week prior to mating and 1x/day during gestation period.
- Necropsy - Males were sacrified at 18 weeks of age and females were sacrificed on GD 21. The following tissues were macroscopically examined: liver, spleen, kidneys, adrenal, heart, lungs, thymus, testes/ovaries, uterus or epididymides. GI tracts from all animals were thoroughly examined grossly. Reproductive organs (testes, epididymides, uterus, ovaries) from ♂ that were not confirmed fertile and ♀ that were not pregnant were fixed in 10 % formalin and subject to histopathological examinations.
- Female Reproductive and Litter Parameters -
  - Nº of copra lutea;
  - Nº of implantation;
  - early deaths (resorption);

- late deaths (macerated or dead fetuses);
- fetal sex determination by estimating the anogenital distance;
- fetal weights;
- fetal external abnormalities;
- fetal visceral (1/3 of fetuses) and skeletal (2/3 of fetuses) abnormalities; and
- placental weight.

Results:

- Clinical Signs and Mortality - There was one death (♂ @ 1 mg/kg/day) as a result of dosing error. Signs of anemic (pale colored eyes, pinnae and limbs) with dark brown feces were observed in 1♂ @ 9 mg/kg (Days 29-65) and 2♀ @ 5 mg/kg (GD 5-9 and 6-13, respectively).
- Body Weights, Food and H_2O Consumption - No treatment-related effects on body weights and food consumption were seen in ♂. A significant ↑ in H_2O consumption was noted in ♂ @ 9 mg/kg on Days 7, 21-28, 42-84 (↑10-28%) and ♀ @ 5 mg/kg on GD 8 (↑14%) and 10 mg/kg (↑19%). Significantly lower mean body weights were noted in ♀ @ 2.5 mg/kg (↓3-10%) and 5.0 mg/kg (↓4-15%) during GD 17-21 and 15-21, respectively. Females @ 5 mg/kg group had slightly but significantly decreased food consumption (↓11-12%) on GD 1, 2 and 4, and increased food consumption on GD 14 and 15 (↑8-10%). Slightly decreased food consumption (↓9-13%) was noted in ♀ @ 2.5 mg/kg on GD 1, 16, 18 and 21. A 7% increase in food intake was observed in ♀ @ 1 mg/kg on GD 9.
- Necropsy - Treatment-caused pathological changes including ulcers, pits, discolored foci, erosion or thinness of mucous layer of the stomach were identified in 3♂ @ 1 mg/kg, 9♂ @ 2.5 mg/kg and 20♂ @ 9 mg/kg but not in any UH-AC 62 XX treated ♀.
- Estrous cycles and Copulation - No effects on estrous rhythms or fertility and copulation indexes were noted.
- Female Reproductive Parameters - A significant reduction in the N⁰ of corpora lutea was noted in ♀ @ 5 mg/kg. At doses ≥2.5 mg/kg, UH-AC 62 XX caused an increased incidence of early resorption and ↓ implantation rates, implantation sites, and N⁰ of live fetuses. The following table summarized the effects of UH-AC 62 XX on female reproductive and fetal paramneters.

Parameters		Control	1.0	2.5	5
N⁰ of Dams sacrificed		24	22	23	24
N⁰ of Corpora Lutea		15.6 ± 1.64	14.7 ± 1.78	14.6 ± 2.04	12.8 ± 1.80**
N⁰ of Implantations		14.8 ± 1.82	13.0 ± 2.79*	10.3 ± 3.24**	5.3 ± 2.40**
Implantation Rate (%)		94.5	88.1	70.1**	41.4**
Total Resorption or Dead Fetuses (%)		6.8	9.2	20.0**	29.1**
Early Resorption (%)		6.3	8.5	20.8**	27.9**
Late Resorption (%)		0.5	0.8	0.0	1.2
Fetal Body Weight (g)	♂	4.98 ± 0.34	5.03 ± 0.33	5.07 ± 0.33	5.50 ± 0.46**
	♀	4.68 ± 0.25	4.79 ± 0.31	4.73 ± 0.29	5.00 ± 0.39**
Placental Weight (g)	♂	0.40 ± 0.05	0.42 ± 0.06	0.46 ± 0.07**	0.55 ± 0.09**
	♀	0.39 ± 0.04	0.42 ± 0.05*	0.46 ± 0.07**	0.51 ± 0.08**

Values expressed as Mean ± SD; * $p<0.05$; ** $p<0.01$.

These effects on reproductive parameters have been commonly seen in animals treated with NSAIDs as a result of reduced prostaglandin biosynthesis. Increased fetal weight observed in fetuses of meloxicam treated dams was due to reduced litter size.

- Fetal External, Visceral and Skeletal Findings - External examinations revealed bilateral anophthalmia in 1/262 fetus at 1 mg/kg and omphalocele in 1/330 @ 0 and 1/92 @ 5 mg/kg groups. In the visceral examination, the following abnormalies were observed: dislocation of esophagus in 1/86 @ 2.5 mg/kg, vascular ring in 1/109 @ 0 and 1/30 @ 5 mg/kg, abnormal origin of left vertebral artery in 1/86 @ 1 mg/kg, ventricular septal defects 3/86 @ 1 mg/kg,

supernumerary right coronary orifice in 1/109 @ 0 mg/kg, and left umbilical artery in 3/109, 1/86, 3/62 and 1/30 fetuses at control, 1, 2.5 and 5 mg/kg, respectively. The incidence of visceral abnormalities was 3.7% (4/109), 5.8% (5/86), 6.5% (4/62), and 3.3% (1/30) for the control, 1, 2.5, and 5 mg/kg, respectively. An increase but not statistical significant in the incidence of skeletal variations was noted in fetuses @ 2.5 and 5 mg/kg as listed in the following table. As shown in the following table, a significant ↓ in the Nº of ossification centers of cervical vertebral bodies was noted for all meloxicam treated groups and the number of ossified sacral and caudal vertebrae was significantly increased in fetuses @ 5 mg/kg.

Parameters		Control	1 mg/kg	2.5 mg/kg	5 mg/kg
Nº of Fetuses Examined (Litters)		221 (24)	176 (22)	133 (23)	62 (23)
Nº of Fetuses with Skeletal Variation (%)		20 (9.0)	17 (9.7%)	16 (12.0%)	11 (17.7%)
Lumbar Rib		13 (5.9%)	6 (3.4%)	6 (4.5%)	7 (11.3%)
Opening of Foramen Transversarium of the 7th Cervical Vertebra		1 (0.5%)	2 (1.1%)	4 (3.0%)	2 (3.2%)
Asymmetrical Sternebrae		3 (1.4%)	3 (1.7%)	2 (1.5%)	2 (3.2%)
Dumbbell Shaped Sternebrae		1 (0.5%)	1 (0.6%)	1 (0.8%)	1 (1.6%)
Nº of Ossification Centers (Mean ± SD)	Cervical Vertebral Body	5.0 ± 0.87	4.4 ± 0.83*	4.5 ± 0.91*	4.2 ±1.21**
	Sacral and Coccygeal Vertebrae	11.6 ± 0.61	11.8 ± 0.91	11.7 ± 0.86	12.1 ± 0.74*

* p<0.05; ** p<0.01.

Therefore, NOEAL for parental toxicity was <1 mg/kg for ♂ and 1 mg/kg for ♀; embryo/fetal developmental toxicity was <1 mg/kg; ♀ reproductive toxicity was 2.5 mg/kg. UH-AC 62 XX was not teratogenic at oral doses up to 5 mg/kg.

2.4.2. *TERATOLOGY (SEGMENT II) STUDIES*

2.4.2.1. U82-0079 Teratogenicity study with the substance UH-AC 62 XX in rats segment-II (Test of organogenesis). 20 December 1982. (Vol. 2.045, p 1)

Report Nº: U82-0079
Study Nº: 38 H
Study Aims: To evaluate the potential of UH-AC 62 XX to induce teratogenic and embryotoxicity following oral administration to pregnant rats.
Compound:
Dose and Route:
Vehicle Control:
Animal: ♀ rats, (SPF), ~10 weeks of age, weighing 230 g, 35/group.
Study Site:
Study Date: 1/11/1982 (Mating Started) - 3/3/1982 (Terminal Sacrifice of F_1)
GLP/QAC Compliance: Yes
Basis of Dose Selection: Results from a subacute toxicity study in rats showed that peptic ulcers occurred at doses ≥3.5 mg/kg and deaths occurred at a dose level of 10 mg/kg. Therefore, 4 mg/kg was set as the high-dose.

Study Design: Pregnant female rats were orally given 0, 1, 2 and 4 mg/kg/day of UH-AC 62 XX from GD 7 to 16. The study was divided into two parts as shown in the following table. Twenty-three ♀ of each group were sacrificed on GD 21 (Part A) and the remaining 12 rats were sacrificed on Day 21 post partum (PPD or PND).

Group	Compound	Dose (mg/kg)	Dosing Period	N° of Rats/Dose	N° of Rats Sacrificed	
					GD 21	PND 21
0	Vehicle Control	0	GD 7→16	35	23	12
1	UH-AC 62 XX	1		35	23	12
2		2		35	23	12
3		4		35	23	12

The following observations were conducted.

- Clinical Signs and Mortality - 2x/day.
- Body Weights - 1x/day on GD 1, 7-16 and 21, PPD 1, 7, 14, and 21.
- Food and H_2O Consumption - Not monitored.
- Necropsy - GD 21 (23♀ from Groups 1-4) and PPD 23-8 (2-7 days after weaning) (12♀ from each group). The following tissues were macroscopically examined: liver, spleen, kidneys, adrenal, heart, lungs, thymus, testes/ovaries, uterus or epididymides. GI tracts from all animals were thoroughly examined grossly. Reproductive organs (testes, epididymides, uterus, ovaries) from ♂ which were not confirmed fertility and ♀ which were not pregnant were fixed in [redacted] and subject to histopathological examinations.
- Female Reproductive and Litter Parameters -

  Part A (C-Section)
  - N° of copra lutea;
  - N° of implantation;
  - % pre-implantation loss;
  - N° of resorption;
  - N° of dead fetuses;
  - N° of live fetuses;
  - fetal sex and sex ratio;
  - N° of abnormalities; and
  - placental weight.

  Part A (Natural Delivery)
  - lenghth of gestation period;
  - N° of implantation;
  - N° of dead fetuses;
  - N° of live fetuses;
  - fetal sex and sex ratio;
  - N° of abnormalities (by macroscopic inspection);
  - mortality: PND 1, 7, 14, and 21; and
  - body weights: PND 1, 7, 14, and 21.
- Observation of F_1 Maturation -
  - PND 13: eruption of the upper incisors;
  - PND 16: development of hair covering;
  - PND 16: opening of auditory canals;
  - PND 18: opening of eyes; and
  - PND 18: correct running, without the trunk touching the ground.
- Function Tests in all F_1 after Weaning -
  - pupillary reflex: Animals were exposed to the beam of 100 watts incandescent bulb and the responses of pupils were observed.
  - righting reflex: Animals were dropped from a highth of 50-60 cm with the backside down and observed whether pups had the ability to turned in the air and land on their feet.
  - hearing ability: Hearing ability was evaluated at frequencies at 80, 150, 800, 4000, and 20000 Hz.

Results:

Effects on F_0

- Clinical Signs and Mortality - Six deaths occurred (1 @ 2 mg/kg on GD 19 and 5 @ 4 mg/kg on GD17-20) with clinical signs of shaggy fur and poor general condition prior to death. One low-dose dam died 7 days after weaning the offspring.
- Body Weights - No treatment-related changes were observed during either gestation or lactation period.
- Necropsy - GI-ulcers were noted in 4/6 rats (1 @ 2 mg/kg and 3 @ 4 mg/kg) that died during pregnancy.
- Female Reproductive and Litter Parameters - There were no abortions and total resorptions observed. The incidence of reproductive and litter parameters are shown in the following table.

Parameter		Control	1 mg/kg	2 mg/kg	4mg/kg
PART A - C-section on GD 21					
Nº of F_0 ♀ Mated		23	23	23	23
Nº of F_0 ♀ Pregnant		19	23	21	21
Nº of Litters Evaluated		19	23	21	16
Corpora Lutea		15.8	14.7	15.7	15.6
Implantations		14.5	13.0*	14.6	14.8
Viable Fetuses		13.7	11.9*	13.6	13.5
Sex (%)	♂	49.3	52.2	53.1	48.8
	♀	50.7	47.8	46.9	51.2
Total Nº of Resorptions		0.7	1.1	1.1	1.3
Fetal Weight (g)		3.7	3.7	3.7	3.9
Preimplantation Loss (%)		8.5	11.0	7.0	5.0
Resorption Rate (%)		5.8	8.6	6.8	9.1
PART A - Natural Delivery					
Nº of F_0 ♀ Mated		12	12	12	12
Nº of F_0 ♀ Pregnant		12	12	12	11
Nº of Litters Evaluated		12	12	12	11
Implantations		13.3	14.1	14.1	13.2
Nº of Newborn/Litter		10.9	13.1	12.3	12.0
Postimplantation Loss (%)		15.9	6.4	13.4	8.5
Sex (%)	♂	57.7	54.1	49.2	51.8
	♀	42.3	45.9	50.8	48.2

* $p<5\%$.

Effects on F_1

- Part A (C-Section) - A total of 10 runts (fetus weighing <65% of the normal weight, ≤2.43 g) were identified: 2 in the control group; 6 @ 1 mg/kg, 3 of which had malformations; and 2 @ 2 mg/kg. A total of 7 litters with 8 malformations were found:
  - control: 2/261 (bifid ribs + fused ribs and waved ribs);
  - 1 mg/kg: 3/274 (meningocele, unilateral absence of the auricle, disorganization of vertebrae);
  - 2 mg/kg: 2/285 (cleft vertebrae).

  The incidence for all observed variations was comparable between the control and UH-AC 62 XX treated group and no apparent dose-relationship was noted.
- Part B (Natural Delivery) - A prolongation of gestation was observed in dams @ 2 and 4 mg/kg. Seven dead offspring were found at parturition (4 @ 0 and 3 @ 2 mg/kg); none had any anomalies. No malformations or variations were detected in the live newborns. Reduced PND 7 survival rate (90.9% vs 94.1% in control) was seen in pups born to dams @ 1 mg/kg. Lower mean body weights (↓5-11%) with reduced body weight gains (↓12-14%) were noted for pups born to dams @ 1 mg/kg during PND 7→21. In addition, delayed development of hair covering and opening of auditory canals were observed in 2-3 pups of 1 mg/kg group.

Therefore, NOEAL for maternal toxicity was 1 mg/kg; reproductive toxicity, 1 mg/kg; embryo/fetal developmental toxicity was <1 mg/kg. UH-AC 62 XX was not teratogenic at oral doses up to 4 mg/kg.

2.4.2.2. U92-0692 Reproduction Studies with meloxicam (UH-AC 62 XX) in Rats Dosed Orally during the Period of Organogenesis (Segment II). 18 March 1992. (Vol. 2.045, p 288)

Study Nº: 359-2324
Report Nº: U92-0692 (Lot Nº 805034[redacted])
Study Aims: To assess the teratogenic potential of UH-AC 62 XX in pregnant rats following oral administration from GD 7→17.
Compound: [redacted]
Dose and Route: [redacted]
Vehicle Control: [redacted]
Animal: Sprague-Dawley Slc:SD rats, 11 weeks of age, weighing 190-249.1 g, 36♀/group.
Study Site: [redacted]
Study Date: 3/26/1991 - 3/18/1992
GLP/QAC Compliance: Yes
Basis of Dose Selection: Results from a pilot study at dose levels of 0, 2, 4, and 6 mg/kg showed that deaths occurred at 6 mg/kg, reduced body weight gains and food consumption with ↑ H_2O intake were noted at 4 mg/kg. Therefore, 4 mg/kg was set as the high-dose for the current study.
Study Design: Pregnant rats were orally dosed with 0, 1, 2 and 4 mg/kg/day of UH-AC 62 XX starting from GD 7 → 17 as presented in the following table.

Group	Compound	Dose (mg/kg)	Dosing Period	Nº of Rats/Dose	Nº of Rats Sacrificed	
					GD 21	PND 21
0	Vehicle Control	0	GD 7→17	36	23	13
1	UH-AC 62 XX	1		36	23	13
2		2		36	23	13
3		4		36	23	13

GD = Gestation Day; PND = Post Natal Day or Post Partum Day.

The following observations were conducted.

- Clinical Signs and Mortality - 2x/day.
- Body Weights and Food/H_2O Consumption - GD 0, 3, 5, 7-17 and PND 0, 4, 7, 14, and 21.
- Necropsy - GD 21 (23♀ from each group) and PND 21 (13♀ from each group). The following tissues were macroscopically examined: liver, spleen, kidneys, adrenal, heart, lungs, thymus, ovaries, and uterus. GI tracts from all animals were thoroughly examined.
- F_0 Female Reproductive and F_1 Litter Parameters -
  - Nº of copra lutea;
  - Nº of implantation;
  - birth index (live birth/implantation sites);
  - early deaths (resorption);
  - late deaths (macerated or dead fetuses);
  - fetal sex determination by estimating the anogenital distance;
  - fetal weights;
  - fetal external abnormalities;
  - fetal visceral (1/3 of fetuses) and skeletal (2/3 of fetuses) abnormalities; and
  - placental weight.
- Neonatal Examination (Natural Delivery) - On PND 4 each litter size was reduced to 4♂ and 4♀ and skeletal examinations were performed on culled pups. The following observations were conducted.
  - gestation period;
  - delivery index [(dam with live newborns/pregnant ♀) x 100];

- litter size;
- stillbirths and live births;
- gross abnormalities;
- pup sex;
- newbon and pup weighst (PND 0, 4, 7, 14, and 21);
- viability index (alive pups on Day 4/liveborn); and
- weaning index (weanings/selected pups on Day 4).

At the end of lactation period (PND 21), 1♂ and 1♀ from each litter were selected for breeding and were evaluated for sense, function and learning ability (during Weeks 4-8). Another pair of 1♂ and 1♀ from each litter was used for reproductive purpose to obtain F_2 (11 weeks of age). The remaining weaned pups were sacrificed and subjected to visceral and skeletal examinations.

- Observation of Maturation - The following functions and abilities were evaluated. **The exact dates to perform the following tests were not indicated in the submission.**
  - erection of pinnae;
  - eruption of incisors;
  - opening of eyelids;
  - appearance of abdominal hair;
  - decent of testes in ♂; and
  - opening of vigina.
- Tests for Development and Fertility of F_1 -
  - sensory function test: On Day 20, reflexes of visual replacing, pain, Preyer, righting, and free fall were evaluated.
  - emotion and motor coordination tests: open-field test, Weeks 4; rota-rod treadmill test, Week 5;
  - learning test: multiple T-maze, Week 6;
  - reproductive capability: mating, Week 11. All males were sacrificed at the end of mating (Week 13). Inseminated F_1 ♀ were weighed every 3 days and sacrificed on GD 21. Female reproductive and litter parameters were evaluated as stated for F_0 females and F_1 fetuses.

Results:

Effects on F_0 Dams

- Mortality and Clinical Signs - No deaths occurred.
- Body Weights, Food Consumption and H_2O Intake - No treatment-related effects were noted.
- Necropsy - At GD 21 sacrifice, gastric ulcers were identified in 4, 7 and 10 dams @ 1, 2, and 4 mg/kg, respectively. Drug-induced GI lesions were also noted in one Group 3 dam that had delivered only stillbirths and was sacrificed on the day of delivery. However, no treatment-caused GI injury was seen in any treated dams that were sacrificed at PND 21.
- Reproductive Performance and Litter Parameters - Increased N⁰ of stillbirths was noted in the dams @ 4 mg/kg. Prolonged gestation period was noted in all UH-AC 62 XX treated group as shown in the following table.

Dose (mg/kg)	N⁰ of Dams Delivered					
	Length of Gestation Period (Day)					
	21.0	21.5	22.0	22.5	23.0	23.5
0	3	10				
1		1	10	2		
2		2	9	2		
4		2	6	2	2	1

The mean incidence of examined fetal and reproductive parameters are listed in the following table.

Parameters		Control	1 mg/kg	2 mg/kg	4 mg/kg
C-Section on GD 21					
Nº of Dams Evaluated		23	23	23	23
Corpora Lutea		15.2	15.3	15.5	14.9
Implantations		13.6	14.7	14.4	14.0
Resorption Rate (%)		8.9	8.6	8.4	9.6
Viable Fetuses		12.3	13.3	13.3	12.7
Sex (♂/♀) Ratio		49/51	50/50	45/55	52/48
Fetal Body Weight	♂	5.00	5.13	5.11	5.21* (4.3%)
	♀	4.69	4.86*	4.84	4.88* (4.1%)
Natural Delivery					
Pregnant F_0 ♂		13	13	13	13
Nº of ♀ with Live Pups		13	13	13	12
Gestation Period (Day)		21.4	22.0**	22.0**	22.3**
Stillbirths (Total)		0	10	3	38*
Viable Pups		13.3	12.0	12.6	11.3
Birth Weight	♂	5.7	6.2** (• 8.8%)	6.3** (• 10.5%)	5.9
	♀	5.3	5.8** (• 9.4%)	5.9** (• 11.3%)	5.6* (• 5.7%)

* $p<0.05$

- Skeletal and Visceral Findings of F_1 Fetuses - There were no treatment-caused increases in the incidence of visceral and skeletal malformations and variations

Effects on F_1 Pups

- Mortality - Reduced 4-day survival rates were observed in the ♂ and ♀ pups of high-dose group and ♀ pups of low-dose group. The mean 4-day survivals for each group are shown in the following table. The survival rates post culling (PND 4) were not affected.

Dose mg/kg	4-Day Survival Rate (%)	
	♂	♀
0	97.4	99.1
1	98.5	92.7
2	97.2	96.9
4	86.7	91.1

- Body Weights - Except ♂ in 4 mg/kg group, newborns of all UH-AC 62 XX treated groups had higher mean birth weights (↑6-11%). In addition, pups from mid- and high-dose groups had significantly higher mean body weights:
  - 2 mg/kg - ♂: ↑7-11% during PND 1→49; ♀: ↑7-12% during PND 1→28;
  - 4 mg/kg - ♂: ↑7% on PND 35; ♀: ↑5-11% during PND 1→21.
- External Findings of F_1 at Birth - The following malformations were observed:
  - Enlarged eyeball - 1/156 @ 1 mg/kg; and
  - crooked tail - 1/147 @ 4 mg/kg.
- Necropsy Findings of F_1 on PND 21 -
  - hepatodiaphragmatic nodule - 1/52 @ 0 and 1/43 @ 4 mg/kg.
- Necropsy Findings of F_1 on PND 56 -
  - accessary spleen - 1/26 @ 2 mg/kg;
  - pitting surface in kidney - 1/20 @ 4 mg/kg;
  - enlarged testes - 1/26 @ 2 mg/kg; and
  - dilation of uterus - 1/26 @ 2 mg/kg and 2/20 @ 4 mg/kg.
- Necropsy Findings of F_1 Involved in Reproduction Fuction Study -
  - hepatodiaphragmatic nodule - 1/26 @ 2 mg/kg and 1/20 @ 4 mg/kg;
  - accessary spleen - 1/20 @ 4 mg/kg;
  - pitting surface in kidney - 1/20 @ 4 mg/kg;

- enlarged testes - 1/20 @ 4 mg/kg;
- fat necrosis - 1/26 @ 0 and 1/26 @ 2 mg/kg; and
- tumor in mammary gland - 1/26 @ 1 mg/kg.

- Maturation and Functional Parameters - Some of examined physical parameters were developed earlier in offspring born to dams treated with UH-AC 62 XX. The significant findings in physical and sensory development in F_1 are presented in the following table.

Physical Development (Days)	Control	1 mg/kg	2 mg/kg	4 mg/kg
N° of F_1 Examined (Litter)	173 (13)	156	164 (13)	147 (12)
Separation of auricle	3.3 ± 0.47	2.8 ± 0.72*	2.5 ± 0.48**	2.5 ± 0.43**
Emergence of hair	9.3 ± 0.63	9.2 ± 0.44	8.8 ± 0.60*	9.5 ± 0.81
Eruption of lower incisor	11.3 ± 0.67	10.8 ± 0.66	10.4 ± 0.62**	10.5 ± 0.86**
Separation of eyelids	15.2 ± 0.72	14.5 ± 1.01	14.5 ± 0.97	13.8 ± 1.13**

- Reflex and Behavior - There were no effects on all examined reflex parameters. In open-field parameters, slight but significant decreases in the number of preening (♂ @ 4 mg/kg, 63. vs 12.5 in control) or rearing (♀ @ 2 and 4 mg/kg - 0.6 and 0.5, respectively vs 1.9 in the control) were observed in the 2 or 4 mg/kg groups. Increases in the number of falls in rotarod treadmill test were noted in the ♂ of 1 mg/kg group (4.0 vs 2.0 in control). The mean values of duration to goal and number of errors in the multiple water T-maze test compared well between the groups with following exceptions: The duration to goal was significantly less in females @ 1 and 4 mg/kg (58.1 and 55 respectively vs 69.9 in control) on the first day of trial, and the duration to goal (327.2 vs 248.8 in control) and number of errors (35.0 vs 25.0 in the control) were increased in ♂ @ 1 mg/kg in the second day of trial.
- Reproductive Functions of F_1 - There were no differences in the between F_1 derived from UH-AC 62 XX treated or control F_0. The incidence of mean reproductive parameters and litter events is summarized in the following table.

Parameter (means)		Control	1 mg/kg	2 mg/kg	4 mg/kg
N° of F_1 Dams Evaluated		13	13	13	11
Corpora Lutea		13.2	14.4	14.7*	13.9
Implantations		12.4	12.2	13.2	12.8
Resorption Rate (%)		5.3	8.0	7.0	5.8
Viable Fetuses	♂	6.2	6.4	6.0	5.4
	♀	5.6	4.8	6.2	6.7
Sex (♂/♀) Ratio		54/46	57/43	50/50	46/54
Fetal Body Weight	♂	5.00	5.04	5.16	4.99
	♀	4.79	4.72	4.83	4.71

- External Examination of F_2 fetuses - No external malformations were identified.

Therefore, NOEAL for maternal toxicity was <1 mg/kg; reproductive toxicity, <1 mg/kg; embryo/fetal developmental toxicity was 2 mg/kg. UH-AC 62 XX was not teratogenic at oral doses up to 4 mg/kg.

2.4.2.3. U82-0078 Teratogenicity study in the rabbit with the substance UH-AC 62 XX segment-II. 24 November 1982. (Vol. 2.046, p 24)

Study N°: 39H
Report N°: U82-0078
Study Aims: To determine the teratogenic potential 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: Rabbits, strain [redacted] (SPF), ~6 months of age, weighing 2300 g, 18/group.