R40

Hoechst

R 40

Dr C. Baeder
Dr W. Weigand
Professor Dr M. Kramer

Hoechst Aktiengesellschaft
Pharma Research
Toxicology

AN ORAL EMBRYOTOXICITY STUDY OF OCTOPIROX IN RABBITS

(Report No. 603/79)

Study No.: G2KO246

October 11, 1979

This report contains the unpublished research findings of Hoechst scientists. It should not be published, in whole or in part, or referred to in any publication without authorisation from the company.

Vorsitzender des Aufsichtsrats Karl Winnacker · Vorstand: Rolf Sammet, Vorsitzender; Kurt Lanz, stellv. Vorsitzender; Erhard Bouillon, Rudolf Frank, Enrique Hartung, Wolfgang Hilger, Willi Hoerkens, Josef Nowotny, Wolfgang von Pölnitz, Hans Reintges, Jürgen Schaafhausen, Hans Schlachter, Klaus Weissermel; stellv.: Martin Frühauf · Sitz der Gesellschaft: Frankfurt am Main · Handelsregister Frankfurt am Main Abt. B Nr. 14500

I N D E X

	Page
Index	1
Summary	2
Survey	3
Introduction	4
Study design and conduct	4 - 6
Results	7 - 9
Tables	
Food intake and body weight	10
Survey of results prior to and at cesarean section	11
Survey of autopsy and skeleton examination results	12
Individual results at cesarean section	13 - 16
Fetal survival rate after 24 hours in the incubator	17 - 18
Explanation of symbols on pp. 13 - 18	19
Autopsy findings in fetuses	20 - 23
Explanation of symbols on pp. 20 - 23	24
Skeleton findings in fetuses	25 - 28
Explanation of symbols on pp. 25 - 28	29
Body and organ weights in dams	30
Statistical methods	31
Control values in previous embryotoxicity studies	32 - 35
Appendices	
Erka® Z 6000 (food composition)	36
GLP statement	37

An oral embryotoxicity study of Octopirox in rabbits

SUMMARY

The antidandruff agent Octopirox was administered by stomach tube in daily single doses of 16, 32, or 63 mg per kg body weight in starch mucilage suspension to groups of 15 pregnant Himalayan rabbits from day 7 to 19 of pregnancy. Simultaneously with this treatment, control animals received the vehicle without drug. On day 29 of pregnancy the dams were killed and delivered, and the fetuses were reared in an incubator for 24 hours and subsequently examined for developmental disorders.

The examinations demonstrated that repeated administration of Octopirox in the sensitive phase of organogenesis caused no impairment of general health status of the dams and no disturbance of intrauterine development of the fetuses.

The examination of the fetuses for developmental status, externally ascertainable abnormalities, visceral and skeletal abnormalities, and a 24-hour viability suggested no embryotoxic and teratogenic action of Octopirox. Two different abnormalities found in 2 different fetuses of the 63 mg/kg group were, according to our observations, spontaneous drug-unrelated events.

S U R V E Y

Study No.:	G2K0246
Drug:	Octopirox (= H 72 6146 A), Batch E 002
Category:	Antidandruff agent
Vehicle:	Starch mucilage
Type of study:	Embryotoxicity study
Animal species:	Rabbit (Himalayan)
Number of animals per group:	15 (pregnant females)
Route of administration:	Oral
Treatment:	13 daily doses from day 7 to 19 of pregnancy
Dosages:	Group 1 : 5 ml starch mucilage per kg body weight (control)
	Group 2 : 16 mg Octopirox per kg body weight
	Group 3 : 32 mg Octopirox per kg body weight
	Group 4 : 63 mg Octopirox per kg body weight
Diet:	Erka®Z 6000 and tap water, both ad libitum
Maintenance:	Singly in metal grill cages
Date of autopsy:	Day 29 of pregnancy
Animal Nos.:	F/1585 - 1644/78
Examination of dams:	Weighing and macroscopic examination of the organs
Examination of fetuses (delivered by cesarean section):	For viability (24 hours in the incubator); in approx. 50 %, autopsy and skeleton analysis; in approx. 50 %, transversal body sections (method of Wilson) and photography
Date of study:	October 23, 1978 - January 2, 1979
Testing facility and archives:	Pharma Research, Hoechst AG, Frankfurt/Main
Responsibilities	
Study director:	Dr C. Baeder
Statistical analysis:	S. Becker-Berger
Industrial toxicology:	Dr W. Weigand
Head of department:	Professor Dr M. Kramer

INTRODUCTION

The antidandruff agent Octopirox (= H 72 6146 A) used in this study came from Batch E 002 (test certificate No. 4714).

In a preceding exploratory oral study, Octopirox was tested in groups of 2 (in the 200 mg/kg group of 3) Himalayan rabbits at dosages of 12.5, 25, 50, 80, 200, or 500 mg per kg body weight from day 7 to 19 after mating. The doses up to 50 mg/kg were tolerated by the dams. At 80 mg/kg 1 dam gave birth before term on day 27 of pregnancy. The second dam of this group showed only implantation sites in the uterus, suggesting abortion or fetal death at an early stage. The dose of 200 mg/kg led to a marked or complete refusal of food, weight reduction, and premature birth between day 25 and 28 of pregnancy in all 3 dams. In the 500 mg/kg group, after a complete refusal of food and severe weight reduction, 1 animal died after the 8th dose and 1 on day 26 of pregnancy. In view of these findings, doses of 16, 32, and 63 mg per kg body weight were selected for this study.

The study was carried out from October, 1978, to January, 1979.

STUDY DESIGN AND CONDUCT

Sexually mature, 6-7-month-old, virgin Himalayan rabbits from our own colonies (Hoe: HIMK (SPF Wiga)), of an initial mean body weight of 2579 ± 162 g, were mated. From day 7 to 19 after mating they received daily single oral doses of

5 ml starch mucilage per kg body weight	- Group 1 (control)
16 mg Octopirox per kg body weight	- Group 2
32 mg Octopirox per kg body weight	- Group 3
63 mg Octopirox per kg body weight	- Group 4

by stomach tube. The drug was suspended in starch mucilage (20 g starch per liter redistilled water) and given in an equal dose volume of 5 ml per kg body weight. Three hours after suspension the drug was shown to be unchanged. The suspensions were

prepared fresh each day. After each weighing of the animals the doses were readjusted.

Fifteen to sixteen females were assigned to each dosage group. They were kept singly under conventional conditions in metal grill cages with wire floors, in a room with a temperature of 21 - 23°C, a 55 - 65% relative humidity, and the change of air 16 - 20 times per hour. The room was illuminated artificially for 12-hour day periods from 6:00 to 18:00 hours, alternating with 12-hour dark night periods. The light intensity measured at a height of 1 meter above the ground in front of the cages was approximately 450 lux.

The diet consisted of Erka®I 6000* and tap water, both supplied ad libitum.

Estrual females were mated with fertile males in the morning, and if sperms were found in the vaginal smear they were caged separately. About 6 hours later they were mated again in case that the first mating might not be successful. The day of mating was taken as day 0 of pregnancy. Pregnancy was regarded as proved if at autopsy implantation sites were demonstrated in the uterus.

(In the following part of the report only pregnant animals will be considered. Omitted will also be 3 dams from the 16 mg/kg group, which died between the 3rd and 7th day of treatment as a result of tracheal gavage).

Throughout the study, the behavior and general health status of the animals were checked daily, food intake continually, and body weight development once a week.

On day 29 after mating all the females were killed by intravenous injection of T 61-Hoechst® and delivered by cesarean section. On opening the uterus, live and dead fetuses, fetal resorption sites, placentae, and corpora lutea on the ovaries were counted and

---

* Produced by Robert Koch oHG, Hamm/Westphalia, Federal Republic of Germany (for composition cf. p. 1[illegible]

macroscopically assessed. Furthermore, the body weight and crown-rump length of the fetuses, the diameter of the conceptuses under resorption, and placental weight were determined. The sex of the fetuses was determined at autopsy.

Subsequently, the fetuses were examined for external appearance and externally ascertainable abnormalities, and reared in an incubator at a temperature of 32°C and a 60% relative humidity for 24 hours. Fetuses which died during this time were recorded. The surviving fetuses were killed with chloroform.

About half of the fetuses in each litter and all prematurely born and dead fetuses - subsequently referred to as skeleton fetuses - were fixed in alcohol, dissected, eviscerated, and cleared in potassium hydroxide. The skeletons were stained with alizarin red S and examined under a magnifying glass for developmental status and abnormalities.

The remaining fetuses - further designated cross-section fetuses - were fixed in Bouin's fluid and examined under a stereomicroscope for organ abnormalities in transversal body sections by the method of Wilson*.

The fetuses were selected for these two types of examination by alternate assignment according to their position in the uterus.

The dams were dissected and their organs were macroscopically assessed. The heart, liver, kidneys, and spleen were weighed. Dams which aborted or littered before term were likewise killed after the event, dissected, and examined for uterine status.

The statistical analysis included simultaneous comparisons of the dosage groups with the control group and comparisons of all groups with the corresponding groups in the previous studies. A list of the statistical methods employed is shown on p. 31.

---

* Described in "Teratology: Principles and Techniques", by J.G.Wilson and J.Warkany, The University of Chicago Press, Chicago and London, 1965.

RESULTS

No unforeseen circumstances were observed which may have affected the quality and integrity of this study.

The behavior and general health status of the dams during the study were unremarkable. All the animals survived the end of the study. A hairless site was found on the throat of 1 dam from the 32 mg/kg group from day 16 of pregnancy, and on the chest of 1 dam from the 63 mg/kg group on day 28 of pregnancy. No causal connection with administration of Octopirox was assumed, since such findings are occasionally encountered in untreated animals.

Food intake was not disturbed by the drug. With the exception of 1 dam from the 63 mg/kg group, which refused food between days 14 and 20 of pregnancy, the amounts consumed in the drug groups corresponded to those consumed in the control group (cf.p. 10).

Likewise the body weight development of the dams was not affected by treatment (cf. p. 10).

The data obtained during pregnancy and on cesarean section are listed on pp. 11 and 13 - 16 . They show that 1 dam in the 16 mg/kg group aborted on day 26 of pregnancy and 1 dam in the 32 mg/kg group littered before term on day 28 of pregnancy. The former animal displayed 9 conceptuses under resorption. The latter produced 8 normally developed live offspring; of 1 offspring only the head was found, the dam having consumed the other parts. The remaining dams in all groups carried live fetuses till delivery. The number of corpora lutea, permitting inference about ovulations after mating, as well as the number of implantations and of live fetuses per litter, lay in all drug groups in the order of magnitude encountered in the simultaneous control group.

Live fetuses in the drug groups were normally developed. Their body weight and crown-rump length corresponded to these parameters in the control group. The sex ratio was balanced in all groups. Dead fetuses were not found in excess of our spontaneous rate. They were markedly underdeveloped, with body weights between 0.31 and 2.79 g. Conceptuses under resorption were fetal primordia with a diameter between 0.69 and 2.64 cm. They were relatively numerous in the control, 32 mg/kg, and 63 mg/kg groups, but there was no difference between the control and drug groups in the frequency of occurrence.

The placentae of live fetuses from the 16 mg/kg and 32 mg/kg groups were unremarkable macroscopically and in respect of weight. In the fetuses from the 63 mg/kg group, placental weights were higher than in the other groups, but they did not exceed the rang of the previous control values and the difference from the simultaneous control was without statistical significance. The placentae of dead fetuses were smaller than those of live fetuses, and anemic.

The survival rate after 24 hours' rearing in the incubator (cf. pp. 17 and 18) corresponded in all drug groups to the survival rate in the simultaneous control group.

Examination of fetuses for abnormalities (cf. pp. 12 , 20 -23 , and 25 - 28) revealed hydrocephalus internus and a cleft palate in 1 fetus from the 63 mg/kg group. Another fetus from this group exhibited a vesicle filled with clear liquid in the skin and muscles dorsal of the lumbar vertebrae, suggesting a locally restricted surface fissure formation.

At autopsy and examination of transversal body sections (cf.pp. 12 and 20 - 23) some fetuses disclosed fused lobes of lung, a transversal and enlarged stomach, a transversal kidney, or an enlarged renal pelvis.

The skeletons of live fetuses delivered to term (cf. pp.12 and 25-28) were found in all drug groups to be at the same stage of development as in the simultaneous control group, corresponding to day 29 of pregnancy. The skeletons of dead fetuses were, in regard to their stage of development, less ossified. In addition to the 2 fetuses of the 63 mg/kg group whose deformities have been described, some fetuses in the drug groups demonstrated a rib on the 7th cervical vertebra, a 13th rib, fused sternebrae, or dislocated/fused caudal vertebral centers, all these being findings also encountered in the control group. Furthermore, 1 control fetus exhibited a dysplastic cervical vertebral arch and 1 control fetus an aplasia of 1 thoracic vertebra and of the corresponding pair of of ribs.

The results of the morphological examinations showed no accumulation of abnormalities and variations in any drug group. The 2 different findings in the 2 fetuses of the 63 mg/kg group are to be viewed in connection with spontaneous deformities of partly the same kind, which were also observed sporadically in other rabbit studies in 1978. Since inquiries into the origin of these abnormalities suggested inheritance from animals of the breed, a causal relation between the findings and the administration of Octopirox was not assumed.

At the autopsy of dams, 1 control dam displayed an enlarged gallbladder, marginal fatty degeneration in 1 lobe of liver, and a lobe of liver fused with the right kidney. Among the drug-treated dams, no macroscopic changes in the internal organs were observed. The weights of the heart, liver, kidneys, and spleen of these animals did not differ from the corresponding weights in the control dams (cf. p. 30).

Dr. Bae/Bi
October 11, 1979

PHARMA FORSCHUNG - TOXIKOLOGIE
Pharma Research - Toxicology
H O E C H S T A G

Signed: Dr C. Baeder
Reproduction toxicology

Signed: Dr W. Weigand
Industrial toxicology

Signed: Professor Dr M. Kramer
Head of department

STUDY:EMBRYOTOXICITY PREPARATION:OCTOPIROX ANIMAL:RABBIT HIMALAYAN
SEX:FEMALE CESAREAN SECTION ON DAY 29 DOSING FROM DAY 7 - 19 POST COPULATIONEM
ROUTE:ORAL VEHICLE:STARCH MUCILAGE
START OF STUDY:10/23/78 STUDY NO:62K0246

DAILY FOOD CONSUMPTION G / 100 G BODY WEIGHT

DOSE	0 - 7				7 -14			14 -20				20 -29			
	DAY OF PREGNANCY														
MG/KG	N	X	S		N	X	S	N	X	S		N	X	S	
CONTROL	11	4.33	0.55	N	10	3.81	0.71	10	3.34	1.26	N	9	3.47	0.75	N
16	14	4.33	0.49	-N	14	3.82	0.43	11	3.02	1.16	-N	10	3.52	0.79	-N
32	14	4.47	0.70	-N	11	3.66	0.47	10	3.33	0.63	-N	7	3.77	0.48	-N
63	10	4.13	0.52	-N	7	3.63	0.49	7	2.76	1.11	-N	7	3.36	0.48	-N

THE FOOD CONSUMPTION IN G/100 G BODY WEIGHT WAS USED FOR THE EVALUATION,FOR DAYS 7-20 THE AREA UNDER THE CURVE.

BODY WEIGHT G

DOSE	0				7			14			20				29			
	DAY OF PREGNANCY																	
MG/KG	N	X	S		N	X	S	N	X	S	N	X	S		N	X	S	
CONTROL	15	2598	150	N	15	2606	130	15	2604	120	15	2622	139	N	15	2752	128	N
16	14	2612	181	-N	14	2627	154	14	2653	152	14	2667	149	-N	14	2810	147	-N
32	14	2532	171	-N	14	2550	145	14	2554	146	14	2610	177	-N	14	2737	199	-N
63	15	2578	161	-N	15	2584	166	15	2588	171	15	2623	174	-N	15	2769	209	-N

THE AREA UNDER THE BODY WEIGHT CURVE WAS USED FOR THE EVALUATION OF DAYS 7-20.

- = NO DIFFERENCE FROM CONTROL (P> .05)
N = WITHIN NORMAL RANGE

* = SIGNIFICANTLY DIFFERENCE FROM CONTROL (P<.05)
A = OUTSIDE NORMAL RANGE

HOECHST AG

PHARMA RESEARCH TOXICOLOGY

STUDY:EMBRYOTOXICITY PREPARATION:OCTOPIROX ANIMAL:RABBIT HIMALAYAN
SEX:FEMALE CESAREAN SECTION ON DAY 29 DOSING FROM DAY 7 - 19 POST COPULATIONEM
ROUTE:ORAL VEHICLE:STARCH MUCILAGE
START OF STUDY:10/23/78 STUDY NO:62K0246

SURVEY OF RESULTS AT CESAREAN SECTION

DOSE MG/KG			CONTROL		16		32		63	
EXPERIMENTAL FEMALES WITH SPERM / PREGNANT			16/15		15/15		15/15		15/15	
PREGNANT FEMALES - WHICH DIED			0		0		0		0	
- WHICH DELIVERED PREMATURELY			0		0		1		0	
- WITH ABORTION OR ONLY EARLY RES			0		1		0		0	
FEMALES ON DAY 29										
- WITH IMPLANTATIONS			15		14		14		15	
- WITH DEAD IMPLANTATIONS ONLY			0		0		0		0	
- WITH LIVE FETUSES			15		14		14		15	
BODY WEIGHT GAIN G (DAY 0- 29)			154		198		205		191	
MEAN NUMBER OF CORPORA LUTEA	+		7.6	N	7.3	-N	7.6	-N	7.5	-N
IMPLANTATIONS	+		6.4	N	7.1	-N	6.6	-N	6.5	-N
RESORPTION SITES	+		1.20	A	0.57	-	1.21	-	1.07	-
DEAD FETUSES	+		0.07	N	0.07	-N	0.07	-N	0.40	-N
LIVE FETUSES	+		5.1	N	6.4	-N	5.4	-N	5.3	-N
RESULTS IN LIVE FETUSES :										
SEX, MALE/FEMALE %			48/52		44/56		55/45		51/49	
BODY WEIGHT G	+	X	43.5	N	42.4	-N	45.1	-N	44.9	-N
		S	3.2		4.6		3.5		3.4	
CROWN-RUMP LENGTH CM	+	X	9.4	N	9.4	-N	9.6	-N	9.5	-N
		S	0.4		0.4		0.5		0.5	
PLACENTAL WEIGHT G	+	X	5.77	N	5.60	-N	5.98	-N	6.22	-N
		S	0.62		0.76		0.57		0.83	
SURVIVAL RATE AFTER 24 HOURS %			97.40	N	94.44	-N	93.33	-N	93.75	-N

+ = STATISTICAL CALCULATION PERFORMED

IF NO SYMBOL IS GIVEN SEE THE TABLE OF PREVIOUS CONTROL VALUES

- = NO DIFFERENCE FROM CONTROL (P>.05)
N = WITHIN NORMAL RANGE
* = SIGNIFICANTLY DIFFERENT FROM CONTROL (P< .05)
A = OUTSIDE NORMAL RANGE

EMBRYOTOXICITY STUDY OF OCTOPIROX IN HIMALAYAN RABBITS

Survey of autopsy and skeleton examination results

Dose on days 7 - 19 of pregnancy	Control	16 mg/kg	32 mg/kg	63 mg/kg
	Number of fetuses (% in brackets)			
Skeleton fetuses				
Number of examined fetuses	43*	49*	48*	50**
Hydrocephalus internus and cleft palate	-	-	-	1 (2.2)
Completely fused middle lobe of right lung with inferior lateral lobe or with superior right lobe	-	3 (6.2)	2 (4.2)	-
Enlarged renal pelves	-	-	-	1 (2.2)
Blood accumulation in thoracic cavity	-	1 (2.0)	-	-
Transversal, or transversal tightly packed, stomach	-	2 (4.1)	4 (8.5)	-
Short or normally long rib on 7th cervical vertebra, unilaterally or bilaterally	1 (2.3)	2 (4.1)	-	4 (9.0)
Dysplastic cervical vertebral arch	1 (2.3)	-	-	-
Short and/or normally long 13th rib, unilaterally or bilaterally	2 (4.7)	2 (4.1)	2 (4.2)	2 (4.5)
Aplastic thoracic vertebra and pair of ribs	1 (2.3)	-	-	-
Fused sternebrae	1 (2.3)	-	-	1 (2.2)
Dislocated or fused caudal vertebral centers	3 (7.1)	-	2 (4.2)	2 (4.5)
Cross-section fetuses				
Number of examined fetuses	35	42	37	36
Transversal, or transversal enlarged, stomach	2 (5.7)	2 (4.8)	-	2 (5.5)
Vesicle filled with clear liquid in the skin and muscles dorsal of lumbar vertebrae	-	-	-	1 (2.7)
Transversal left kidney	2 (5.7)	1 (2.3)	1 (2.7)	3 (8.3)

Of this number *1, **6 stunted dead fetuses omitted in mean values

HOECHST AG PHARMA RESEARCH TOXICOLOGY

STUDY:EMBRYOTOXICITY PREPARATION:OCTOPIROX ANIMAL:RABBIT HIMALAYAN
SEX:FEMALE CESAREAN SECTION ON DAY 29 DOSING FROM DAY 7 - 19 POST COPULATIONEM
ROUTE:ORAL VEHICLE:STARCH MUCILAGE
START OF STUDY:10/23/78 STUDY NO:G2K0246

INDIVIDUAL RESULTS AT CESAREAN SECTION

DOSE: CONTROL START OF STUDY THIS GROUP: 10/23/78

NO. F/78	DAM BW GAIN G DAY 0-29	CORP. LUT	IMPLANTATIONS TOT-AL	LIVE	DEAD	RES	SEX M	SEX F	LIVE FETUSES BODY-WEIGHT G N	X	S	CROWN-RUMP LENGTH CM N	X	S	PLACENTAL WEIGHT G N	X	S	REMARKS
1585	120	9	6	6	0	0	4	2	6	45.93	2.24	6	9.98	0.40	6	6.26	0.85	
1586	75	6	5	5	0	0	0	5	5	44.72	1.09	5	9.04	0.11	5	5.59	0.32	
1587	240	9	8	8	0	1	0	8	8	43.52	1.76	8	9.10	0.23	8	5.78	0.53	-
1588	300	8	8	8	0	0	5	3	8	34.01	3.74	8	9.15	0.41	8	4.14	0.50	-
1589	290	8	8	8	0	0	7	1	8	42.11	1.74	8	9.65	0.19	8	6.10	0.71	-
1590	80	7	6	5	0	1	3	2	5	44.98	1.37	5	9.70	0.16	5	5.77	0.72	-
1591	110	7	4	4	0	0	2	2	4	44.77	2.30	4	9.37	0.25	4	6.57	0.81	-
1592	215	7	5	5	0	0	3	2	5	43.88	2.77	5	9.32	0.15	5	6.00	0.72	-
1593	80	7	7	7	0	0	4	3	7	43.54	2.91	7	9.26	0.21	7	5.09	0.93	a
1594	-30	5	5	1	0	4	1	0	1	46.00	0.00	1	9.90	0.00	1	5.49	0.00	-
1595	260	7	7	4	1	2	1	3	4	43.55	1.91	4	8.70	0.36	4	5.49	0.69	b
1596	420	14	7	7	0	0	4	3	7	42.91	3.15	7	10.06	0.31	7	5.65	0.86	-
1597	-30	8	7	2	0	5	0	2	2	48.05	0.78	2	8.95	0.07	2	6.45	0.19	-
1598	115	6	6	4	0	2	2	2	4	45.02	3.98	4	9.80	0.37	4	6.44	0.71	-
1599	70	5	5	3	0	3	1	2	3	40.27	13.77	3	8.80	1.31	3	5.66	1.71	-
N	15	114	96	77	1	18	37	40	77			77			77			
X	154	7.6	6.4	5.1	0.07	1.20	2.5	2.7		43.52			9.39			5.77		
S	128										3.19			0.44			0.62	

Explanation of symbols follows

MULCHST 76 PHARMA RESEARCH TOXICOLOGY

STUDY:EMBRYOTOXICITY PREPARATION:OCTOPIROX ANIMAL:RABBIT HIMALAYAN
SEX:FEMALE CESAREAN SECTION ON DAY 29 DOSING FROM DAY 7 - 19 POST COPULATIONEM
ROUTE:ORAL VEHICLE:STARCH MUCILAGE
START OF STUDY:10/23/78 STUDY NO:G2K0246

INDIVIDUAL RESULTS AT CESAREAN SECTION

DOSE: 15 MG/KG START OF STUDY THIS GROUP: 10/23/78

NO. F78	DAM BW GAIN G DAY 0-29	CORP. LUT	IMPLANTATIONS TOT-AL	LIVE	DEAD	RES	SEX M	SEX F	LIVE FETUSES BODY-WEIGHT G N	X	S	CROWN-RUMP LENGTH CM N	X	S	PLACENTAL WEIGHT G N	X	S	REMARKS
1600	340	7	6	6	0	0	4	2	6	46.52	4.21	6	10.08	0.43	6	6.26	0.85	-
1601	380	8	8	6	0	0	3	5	8	41.05	3.05	8	9.29	0.42	8	4.90	0.50	-
1602	270	7	7	7	0	0	3	4	7	44.89	2.50	7	9.71	0.31	7	4.98	0.68	-
1603	[illegible]	8	7	5	0	2	2	3	5	43.26	3.69	5	9.76	0.32	5	5.93	1.08	-
1604	210	8	8	6	0	2	2	4	6	44.70	4.72	6	9.55	0.31	6	6.80	1.16	-
1605	160	5	5	5	0	0	4	1	5	43.12	3.00	5	9.66	0.25	5	5.95	0.81	-
1606	300	7	7	7	0	0	3	4	7	44.09	2.23	7	9.19	0.32	7	5.41	0.57	-
1607	240	8	8	8	0	0	3	5	8	41.05	4.36	8	9.02	0.35	8	5.30	0.85	-
1608**	55	9	9															** c
1609	45	4	4	4	0	0	2	2	4	48.02	0.96	4	9.52	0.10	4	6.78	0.59	-
1610	145	6	6	3	0	3	3	0	3	46.40	3.44	3	9.33	0.12	3	6.31	1.15	-
1611	60	8	8	8	0	0	4	4	8	33.31	7.32	8	9.05	0.81	8	4.95	0.94	-
1612	-10	9	8	7	1	0	4	3	7	33.66	7.12	7	8.89	0.60	7	4.79	0.79	d
1613	290	9	9	8	0	1	2	6	8	45.22	3.94	8	9.66	0.23	8	5.71	0.84	-
1614	340	8	8	8	0	0	1	7	8	38.07	7.01	8	9.22	0.59	8	4.39	0.70	-
N	14	102	99	90	1	8	40	50	90			90			90			
X	198	7.3	7.1	6.4	0.07	0.57	2.9	3.6		42.38			9.45			5.60		
S	132										4.55			0.36			0.76	

Explanation of symbols follows

STUDY:EMBRYOTOXICITY PREPARATION:OCTOPIROX ANIMAL:RABBIT HIMALAYAN
SEX:FEMALE CESAREAN SECTION ON DAY 29 DOSING FROM DAY 7 - 19 POST COPULATIONEM
ROUTE:ORAL VEHICLE:STARCH MUCILAGE
START OF STUDY:10/23/78 STUDY NO:G2K0246

INDIVIDUAL RESULTS AT CESAREAN SECTION

DOSE: 32 MG/KG START OF STUDY THIS GROUP: 10/23/78

NO. F/78	DAM BW GAIN G DAY 6-29	CORP. LUT	IMPLANTATIONS TOT-AL	LIVE	DEAD	RES	SEX M	SEX F	LIVE FETUSES BODY-WEIGHT G N	X	S	CROWN-RUMP LENGTH CM N	X	S	PLACENTAL WEIGHT G N	X	S	REMARKS
1615	170	9	4	3	0	1	2	1	3	44.60	1.22	3	9.83	0.23	3	5.86	0.58	-
1616	300	9	9	9	0	0	6	3	9	39.84	2.01	9	8.50	0.19	9	4.87	0.52	-
1617	135	8	7	7	0	0	3	4	7	49.07	3.59	7	9.27	0.16	7	6.04	0.87	-
1618	165	5	5	4	0	1	2	2	4	45.40	6.36	4	10.00	0.43	4	6.47	1.33	-
1619	175	7	7	5	1	1	2	3	5	52.74	4.24	5	10.40	0.30	5	6.50	0.79	0
1620	110	6	6	3	0	3	0	3	3	44.80	1.04	3	9.83	0.25	3	6.48	0.27	-
1621	220	7	6	4	0	2	3	1	4	46.32	2.16	4	10.27	0.33	4	6.72	1.20	-
1622	135	5	5	4	0	1	3	1	4	42.45	3.41	4	9.10	0.42	4	5.38	0.99	-
1623	120	8	8	6	0	2	5	1	6	42.45	2.96	6	9.08	0.21	6	5.98	0.70	-
1624	70	6	6	3	0	3	2	1	3	48.30	2.26	3	9.37	0.15	3	6.15	0.93	-
1625	260	8	8	8	0	0	6	2	8	40.61	3.30	8	9.57	0.41	8	5.36	0.72	-
1626	250	7	6	3	0	3	2	1	3	48.30	3.47	3	9.67	0.32	3	6.29	0.35	-
1627	390	8	8	8	0	0	3	5	8	43.70	2.98	8	9.24	0.24	8	5.55	0.70	-
1628	370	11	8	8	0	0	2	6	8	43.49	1.36	8	10.05	0.28	8	5.08	0.55	-
1629**	40	9	9															** [
N	14	107	93	75	1	17	41	34	75			75			75			
X	205	7.6	8.6	5.4	0.07	1.21	2.9	2.4		45.15			9.59			5.98		
S	97										3.54			0.53			0.57	

Explanation of symbols follows

HOECHST AG PHARMA RESEARCH TOXICOLOGY

STUDY:EMBRYOTOXICITY PREPARATION:OCTOPIROX ANIMAL:RABBIT HIMALAYAN
SEX:FEMALE CESAREAN SECTION ON DAY 29 DOSING FROM DAY 7 - 19 POST COPULATIONEM
ROUTE:ORAL VEHICLE:STARCH MUCILAGE
START OF STUDY:10/23/78 STUDY NO:62K0246

INDIVIDUAL RESULTS AT CESAREAN SECTION

DOSE: 73 MG/KG START OF STUDY THIS GROUP: 10/23/78

NO. F/78	DAM BW GAIN G DAY 0-29	CORP. LUT	IMPLANTATIONS TOT-AL	LIVE	DEAD	RES	SEX M	SEX F	LIVE FETUSES BODY-WEIGHT G N	X	S	CROWN-RUMP LENGTH CM N	X	S	PLACENTAL WEIGHT G N	X	S	REMARKS
1630	435	8	8	8	0	0	1	7	8	42.82	8.91	8	9.69	0.67	8	4.80	1.24	-
1631	130	6	6	5	0	1	2	3	5	45.42	3.43	5	9.28	0.40	5	5.69	0.61	-
1632	30	5	4	4	0	0	3	1	4	45.17	0.91	4	8.92	0.13	4	6.31	0.25	-
1633	-130	6	6	1	5	0	1	0	1	46.60	0.00	1	10.10	0.00	1	7.72	0.00	-
1634	470	9	9	9	0	0	5	4	9	45.71	3.51	9	10.03	0.34	9	5.87	0.74	-
1635	265	11	9	8	0	1	3	5	8	42.30	4.63	8	9.62	0.30	8	6.02	0.79	-
1636	240	9	8	7	0	1	4	3	7	42.33	7.08	7	9.59	0.72	7	5.96	1.37	-
1637	290	10	10	4	0	6	2	2	4	49.42	4.00	4	9.57	0.51	4	6.20	0.97	-
1638	370	8	8	8	0	0	5	3	8	42.87	2.21	8	9.21	0.18	3	5.08	0.75	-
1639	210	8	8	6	1	1	2	4	6	40.98	3.83	6	9.27	0.36	6	5.11	0.50	-
1640	135	4	4	3	0	1	2	1	3	48.73	4.85	3	10.00	0.20	3	6.66	1.08	-
1641	145	8	5	3	0	2	3	0	3	47.93	1.99	3	9.57	0.38	3	7.02	0.26	-
1642	100	7	7	7	0	0	5	2	7	38.93	4.95	7	8.89	0.43	7	6.58	1.38	-
1643	150	8	6	6	0	0	2	4	6	43.77	3.49	6	10.00	0.37	6	5.94	0.72	-
1644	-40	7	4	1	0	3	1	0	1	51.10	0.00	1	8.60	0.00	1	7.34	0.00	-
N	15	114	102	80	6	16	41	39	80			80			80			
X	191	7.6	6.8	5.3	0.40	1.07	2.7	2.6		44.94			9.49			6.22		
S	195										3.39			0.46			0.83	

Explanation of symbols follows

HOECHST AG

PHARMA RESEARCH TOXICOLOGY

STUDY:EMBRYOTOXICITY
PREPARATION:OCTOPIROX
ANIMAL:RABBIT HIMALAYAN
SEX:FEMALE
CESAREAN SECTION ON DAY 29
DOSING FROM DAY 7 - 19 POST COPULATIONEM
ROUTE:ORAL
VEHICLE:STARCH MUCILAGE
START OF STUDY:10/23/78
STUDY NO:G2K0246

FETAL SURVIVAL RATE IN INCUBATOR UP TO 24 HOURS AFTER CESAREAN SECTION

SURVIVAL RATE = NUMBER LIVE FETUSES 24 HOURS AFTER CESAREAN SECTION / NUMBER LIVE FETUSES AT CESAREAN SECTION %

DOSE : CONTROL

DAM NO F/78	NUMBER AT BIRTH LIVE	NUMBER AT BIRTH DEAD	NUMBER DEAD FETUSES 0-1 HOURS AFTER BIRTH	1-2	2-3	3-4	4-24	SURVIVAL RATE %
1585	6							100.0
1586	5							100.0
1587	8							100.0
1588	8						1	87.5
1589	8							100.0
1590	5							100.0
1591	4							100.0
1592	5							100.0
1593	7							100.0
1594	1							100.0
1595	4	1						100.0
1596	7			1				85.7
1597	2							100.0
1598	4							100.0
1599	3							100.0
SUM	77	1		1			1	97.4

DOSE : 16 MG/KG

DAM NO F/78	NUMBER AT BIRTH LIVE	NUMBER AT BIRTH DEAD	NUMBER DEAD FETUSES 0-1 HOURS AFTER BIRTH	1-2	2-3	3-4	4-24	SURVIVAL RATE %
1600	6							100.0
1601	8							100.0
1602	7							100.0
1603	5							100.0
1604	6						1	83.3
1605	5							100.0
1606	7						1	85.7
1607	5							100.0
1608	**							C
1609	4							100.0
1610	3						1	66.7
1611	8			1				87.5
1612	7	1						100.0
1613	8							100.0
1614	8			1				87.5
SUM	90	1		2			3	94.4

Explanation of symbols follows

STUDY:EMBRYOTOXICITY PREPARATION:OCTOPIROX ANIMAL:RABBIT HIMALAYAN
SEX:FEMALE CESAREAN SECTION ON DAY 29 DOSING FROM DAY 7 - 19 POST COPULATIONFM
ROUTE:ORAL VEHICLE:STARCH MUCILAGE
START OF STUDY:10/23/78 STUDY NO:G2K0246

FETAL SURVIVAL RATE IN INCUBATOR UP TO 24 HOURS AFTER CESAREAN SECTION

SURVIVAL RATE = NUMBER LIVE FETUSES 24 HOURS AFTER CESAREAN SECTION / NUMBER LIVE FETUSES AT CESAREAN SECTION %

DOSE : 32 MG/KG

DAM NO F/78	NUMBER AT BIRTH LIVE	NUMBER AT BIRTH DEAD	NUMBER DEAD FETUSES 0-1 HOURS AFTER BIRTH	1-2	2-3	3-4	4-24	SURVIVAL RATE %
1615	3			2				33.3
1616	9							100.0
1617	7							100.0
1618	4							100.0
1619	5	1						100.0
1620	3			1				66.7
1621	4							100.0
1622	4						1	75.0
1623	6			1				83.3
1624	3							100.0
1625	8							100.0
1626	3							100.0
1627	8							100.0
1628	8							100.0
1629	**							f
SUM	75	1		4			1	93.3

DOSE : 63 MG/KG

DAM NO F/78	NUMBER AT BIRTH LIVE	NUMBER AT BIRTH DEAD	NUMBER DEAD FETUSES 0-1 HOURS AFTER BIRTH	1-2	2-3	3-4	4-24	SURVIVAL RATE %
1630	8							100.0
1631	5							100.0
1632	4							100.0
1633	1	5					1	0.0
1634	9							100.0
1635	8			1				87.5
1636	7							100.0
1637	4		1					75.0
1638	8							100.0
1639	6	1				1		83.3
1640	3							100.0
1641	3							100.0
1642	7						1	85.7
1643	6							100.0
1644	1							100.0
SUM	80	6	1	1		1	2	93.8

Explanation of symbols follows

EMBRYOTOXICITY STUDY OF OCTOPIROX IN HIMALAYAN RABBITS

Explanation of symbols on pp. 13 - 18.

---

a Dam with markedly enlarged gallbladder; marginal fatty degeneration in right lobe of liver and right caudate lobe of liver fused with right kidney

b 1 stunted dead female fetus; body weight (2.79 g), crown-rump length (4.36 cm), and placental weight (3.17 g) omitted in mean values

c Dam aborted on day 26 of pregnancy; 9 conceptuses under resorption

d 1 stunted dead fetus; sex impossible to determine; body weight (1.31 g), crown-rump length (3.1 cm), and placental weight (2.97 g) omitted in mean values

e 1 stunted dead fetus; sex impossible to determine; body weight (1.61 g), crown-rump length (3.9 cm), and placental weight (3.20 g) omitted in mean values

f Premature birth on day 28 of pregnancy; 1 live offspring and head of another offspring found on cage floor; 6 live fetuses in uterus and 1 live fetus in birth canal: body weight (32.8 - 39.0 g), crown-rump length (8.9 - 9.5 cm), and placental weight (4.45 - 7.30 g) omitted in mean values

g 5 stunted dead fetuses; sex impossible to determine; body weight (0.31 - 0.36 g), crown-rump length (2.1 - 2.6 cm), and placental weight (1.93 - 3.89 g) omitted in mean values

h 1 stunted dead fetus; sex impossible to determine; body weight (1.12 g), crown-rump length (2.95 cm), and placental weight (1.88 g) omitted in mean values

** abortion or premature birth

EMBRYOTOXICITY STUDY

Findings in fetuses at autopsy

Compound: starch mucilage (control)

Dose: 5 ml/kg

Route: oral

Animal: Himalayan rabbit

DAM No. F/78	FETUSES at delivery live	dead	m	f	examined for skeletal abnormality number examined	sex m	f	findings	examined for soft-tissue abnormality number examined	sex m	f	findings
1585	6	0	4	2	3	1	2	N.A.D.	3	3	0	1m
1586	5	0	0	5	3	0	3	N.A.D.	2	0	2	N.A.D.
1587	8	0	0	8	4	0	4	N.A.D.	4	0	4	N.A.D.
1588	8	0	5	3	4	3	1	N.A.D.	4	2	2	N.A.D.
1589	8	0	7	1	4	4	0	N.A.D.	4	3	1	1m
1590	5	0	3	2	3	2	1	N.A.D.	2	1	1	N.A.D.
1591	4	0	2	2	2	1	1	N.A.D.	2	1	1	N.A.D.
1592	5	0	3	2	3	2	1	N.A.D.	2	1	1	N.A.D.
1593	7	0	4	3	4	3	1	N.A.D.	3	1	2	N.A.D.
1594	1	0	1	0	1	1	0	N.A.D.				
1595	4	1	1	4	3	0	3	1a	2	1	1	N.A.D.
1596	7	0	4	3	4	2	2	N.A.D.	3	2	1	1b
1597	2	0	0	2	1	0	1	N.A.D.	1	0	1	N.A.D.
1598	4	0	2	2	2	1	1	N.A.D.	2	1	1	1i
1599	3	0	1	2	2	1	1	N.A.D.	1	0	1	N.A.D.
n	77	1	37	41	43	21	22		35	16	19	

Explanation of symbols follows

EMBRYOTOXICITY STUDY

Findings in fetuses at autopsy

Compound: Octopirox

Dose: 16 mg/kg

Route: oral

Animal: Himalayan rabbit

DAM No. F/ 78	FETUSES at delivery live	dead	m	f	examined for skeletal abnormality number examined	sex m	f	findings	examined for soft-tissue abnormality number examined	sex m	f	findings
1600	6	0	4	2	3	2	1	N.A.D.	3	2	1	N.A.D.
1601	8	0	5	5	4	1	3	1e	4	2	2	N.A.D.
1602	7	0	5	4	4	2	2	N.A.D.	3	1	2	N.A.D.
1603	5	0	2	3	3	1	2	1e	2	1	1	N.A.D.
1604	6	0	2	4	3	1	2	N.A.D.	3	1	2	N.A.D.
1605	5	0	4	1	3	3	0	N.A.D.	2	1	1	N.A.D.
1606	7	0	3	4	4	1	3	1h	3	2	1	1m
1607	8	0	5	5	4	1	3	N.A.D.	4	2	2	1h
1609	4	0	2	2	2	2	0	N.A.D.	2	0	2	N.A.D.
1610	3	0	3	0	2	2	0	N.A.D.	1	1	0	N.A.D.
1611	8	0	4	4	4	1	3	N.A.D.	4	3	1	1i
1612	7	1	4	3	5	2	2	1b	3	2	1	N.A.D.
1613	8	0	2	6	4	1	3	1fh	4	1	3	N.A.D.
1614	8	0	1	7	4	0	4	1g	4	1	3	N.A.D.
n	90	1	40	50	49	20	28		42	20	22	

Explanation of symbols fol ws

EMBRYOTOXICITY STUDY

Findings in fetuses at autopsy

Compound: Octopirox

Dose: 32 mg/kg

Route: oral

Animal: Himalayan rabbit

DAM No. P/78	FETUSES at delivery live	dead	m	f	examined for skeletal abnormality number examined	sex m	f	findings	examined for soft-tissue abnormality number examined	sex m	f	findings
1615	3	0	2	1	2	2	0	N.A.D.	1	0	1	N.A.D.
1616	9	0	6	3	5	2	3	N.A.D.	4	4	0	N.A.D.
1617	7	0	3	4	4	2	2	N.A.D.	3	1	2	N.A.D.
1618	4	0	2	2	2	0	2	N.A.D.	2	2	0	N.A.D.
1619	5	1	2	3	4	2	1	1b	2	0	2	N.A.D.
1620	3	0	0	3	2	0	2	1e	1	0	1	N.A.D.
1621	4	0	3	1	2	1	1	N.A.D.	2	2	0	N.A.D.
1622	4	0	3	1	2	2	0	N.A.D.	2	1	1	N.A.D.
1623	6	0	5	1	3	3	0	1h	3	2	1	1m
1624	3	0	2	1	2	2	0	N.A.D.	1	0	1	N.A.D.
1625	8	0	6	2	4	3	1	N.A.D.	4	3	1	N.A.D.
1626	3	0	2	1	2	2	0	N.A.D.	1	0	1	N.A.D.
1627	8	0	3	5	4	2	2	N.A.D.	4	1	3	N.A.D.
1628	8	0	2	6	4	1	3	1e	4	1	3	N.A.D.
1629	8r	1	5	2	6	3	1	2h, 1hk, 2r	3	2	1	N.A.D.
n	85	2	46	36	48	27	18		37	19	18	

Explanation of symbols foll s

EMBRYOTOXICITY STUDY

Findings in fetuses at autopsy

Compound: Octoprox

Dose: 63 mg/kg

Route: oral

Animal: Himalayan rabbit

DAM No. F/78	FETUSES at delivery live	dead	m	f	examined for skeletal abnormality number examined	sex m	f	findings	examined for soft-tissue abnormality number examined	sex m	f	findings
1630	8	0	1	7	4	1	3	1n	4	0	4	1d
1631	5	0	2	3	3	1	2	N.A.D.	2	1	1	1m
1632	4	0	3	1	2	1	1	N.A.D.	2	2	0	N.A.D.
1633	1	5	1	0	6	1	0	5b				
1634	9	0	5	4	5	4	1	N.A.D.	4	1	3	N.A.D.
1635	8	0	3	5	4	1	3	1c	4	2	2	1m
1636	7	0	4	3	4	2	2	N.A.D.	3	2	1	N.A.D.
1637	4	0	2	2	2	1	1	N.A.D.	2	1	1	1m
1638	8	0	5	3	4	2	2	N.A.D.	4	3	1	1h
1639	6	1	2	4	4	1	2	1b	3	1	2	N.A.D.
1640	3	0	2	1	2	1	1	N.A.D.	1	1	0	N.A.D.
1641	3	0	3	0	2	2	0	N.A.D.	1	1	0	N.A.D.
1642	7	0	5	2	4	3	1	N.A.D.	3	2	1	1hi
1643	6	0	2	4	3	1	2	N.A.D.	3	1	2	N.A.D.
1644	1	0	1	0	1	1	0	N.A.D.				
n	80	6	41	39	50	23	21		36	18	18	

Explanation of symbols follows

EMBRYOTOXICITY STUDY OF OCTOPIROX IN HIMALAYAN RABBITS

Explanation of symbols on pp. 20 - 23

(The figure preceding the symbol indicates the number of fetuses)

a Stunted dead fetus

b Stunted dead fetus; determination of sex and assessment of organs impossible because of small size

c Hydrocephalus internus; cleft palate

d Vesicle (approx. 0.6 cm in diameter) filled with clear liquid in skin and muscles dorsal of lumbar vertebrae

e Middle lobe of right lung completely fused with inferior lateral lobe

f Middle lobe of right lung completely fused with superior right lobe

g Blood accumulation in thoracic cavity

h Transversal stomach

i Enlarged stomach

k Tightly packed stomach

m Transversal left kidney

n Enlarged renal pelves

r Offspring from premature birth on day 28 of pregnancy; 2 offspring not examined

EMBRYOTOXICITY STUDY

Examination for skeletal abnormalities

Compound: starch mucilage (control)

Dose: 5 ml/kg

Route: oral

Animal: Himalayan rabbit

DAT No. F/78	No. of fetuses	Head	Cervical vertebrae 0-6	Cervical vertebrae 7	Thoracic vertebrae 0-12	Thoracic vertebrae 13	Sternum (sternebrae) 0-4	Sternum (sternebrae) 5	Sternum (sternebrae) 6	Ribs 0-11	Ribs 12	Ribs 13	Cervical ribs	Lumbar vertebrae 0-5	Lumbar vertebrae 6	Lumbar vertebrae 7	Sacral vertebrae 0-5	Sacral vertebrae 6	Caudal vertebrae $\bar{x}$	Fragm. vertebral centra	Extremities ossification of metacarpal 1 Yes	Extremities ossification of metacarpal 1 No	Remainder of skeleton
1585	3	N.A.D.		3		3		1	2		3		-		3			3	13.3	-	3	0	N.A.D.
1586	3	N.A.D.		3		3			3		3		-		3			3	12.7	-	3	0	N.A.D.
1587	4	N.A.D.		4		4			4		2	1f 1g	-		4			4	13.2	-	4	0	N.A.D.
1588	4	N.A.D.		4		4		2	1 1i		4		-		4			4	12.0	-	1	0	N.A.D.
1589	4	N.A.D.		1		4			4		4		-		4			4	12.5	-	4	0	N.A.D.
1590	3	N.A.D.		2 1e		3			3		3		-		3			3	13.3 1k	-	3	0	N.A.D.
1591	2	N.A.D.		2		2		1	1		2		-		2			2	13.0	-	2	0	N.A.D.
1592	3	N.A.D.		3		3		3			3		-		3			3	13.0	-	3	0	N.A.D.
1593	4	N.A.D.		4		4			4		4		-		4			4	13.5 1k	-	4	0	N.A.D.
1594	1	N.A.D.		1	1h			1		1h			-		1			1	13.0	-	1	0	N.A.D.
1595	3	1a	1	2	1	2	1		2	1	2		-	1	2		1	2	13.5 1k	-	2	1	1a
1596	4	N.A.D.		4		4		2	2		4		-		4			4	12.7	-	1	0	N.A.D.
1597	1	N.A.D.		1		1			1		1		-		1			1	15.0	-	1	0	N.A.D.
1598	2	N.A.D.		2		2		2			2		1c		2			2	13.0	-	2	0	N.A.D.
1599	2	N.A.D.		2		2			2		2		-		2			2	12.5	-	2	0	N.A.D.

Explanations of symbols follo

EMBRYOTOXICITY STUDY

Examination for skeletal abnormalities

Compound: Octopirox

Dose: 16 mg/kg

Route: oral

Animal: Himalayan rabbit

DM1 No. F/ 78	No. of fetuses	Head	Cervical vertebrae		Thoracic vertebrae		Sternum (sternebrae)			Ribs			Cervical ribs	Lumbar vertebrae		Sacral vertebrae		Caudal vertebrae	Fragm. vertebral centra	Extremities ossification of metacarpal Yes	No	Remainder of skeleton
			0-6	7	0-12	13	0-4	5	6	0-11	12	13		0-5	6	7	0-5	6	$\bar{x}$			
1600	3	N.A.D.		3		3			3		3		1c		3			3	12.7	-	3	0	N.A.D.
1601	4	N.A.D.		4		4			4		4		-		4			4	13.2	-	4	0	N.A.D.
1602	4	N.A.D.		4		4		4			4		-		4			4	12.7	-	4	0	N.A.D.
1603	3	N.A.D.		3		3			3		3		-		3			3	13.3	-	3	0	N.A.D.
1604	3	N.A.D.		3		3			3		3		-		3			3	13.7	-	3	0	N.A.D.
1605	3	N.A.D.		3		3		1	2		3		-		3			3	13.3	-	3	0	N.A.D.
1606	4	N.A.D.		4		4		1	3		4		1c		4			4	13.0	-	4	0	N.A.D.
1607	4	N.A.D.		4		4			4		4		-		4			4	12.5	-	4	0	N.A.D.
1609	2	N.A.D.		2		2			2		2		-		2			2	13.5	-	2	0	N.A.D.
1610	2	N.A.D.		2		2			2		1	1g	-		2			2	13.5	-	2	0	N.A.D.
1611	4	N.A.D.		4		4		4			4		-	2	2			4	12.7	-	4	0	N.A.D.
1612	5	1a	1	4	1	4	1	2	2	1	3	1g	-	1	4		1	4	12.7	-	4	1	1a
1613	4	N.A.D.		4		4			4		4		-		4			4	13.5	-	4	0	N.A.D.
1614	4	N.A.D.		4		4		2	2		4		-		4			4	13.2	-	4	0	N.A.D.

Explanation of symbols follows

EMBRYOTOXICITY STUDY

Examination for skeletal abnormalities

Compound: Octopirox

Dose: 32 mg/kg

Animal: Himalayan rabbit

Route: oral

DM No. 1/78	No. of fetuses	Head	Cervical vertebrae		Thoracic vertebrae		Sternum (sternebrae)			Ribs			Cervical ribs	Lumbar vertebrae			Sacral vertebrae		Caudal vertebrae	Fragm. vertebral centra	Extremities ossification of metacarpal		Remainder of skeleton
																					Yes	No	
			0-6	7	0-12	13	0-4	5	6	0-11	12	13		0-5	6	7	0-5	6	$\bar{x}$				
1615	2	N.A.D.		2		2		1	1		2		-		2			2	13.5	-	2	0	N.A.D.
1616	5	N.A.D.		5		5		1	4		5		-		5			5	12.6	-	5	0	N.A.D.
1617	4	N.A.D.		4		4			4		4		-		4			4	1k 13.2	-	4	0	N.A.D.
1618	2	N.A.D.		2		2		1	1		2		-		2			2	1k 12.5	-	2	0	N.A.D.
1619	4	1a	1	3	1	3	1		3	1	3		-	1	3		1	3	13.0	-	3	1	1a
1620	2	N.A.D.		2		2			2		2		-		2			2	13.0	-	2	0	N.A.D.
1621	2	N.A.D.		2		2		1	1		2		-		2			2	12.0	-	2	0	N.A.D.
1622	2	N.A.D.		2		2		1	1		2		-		2			2	12.0	-	2	0	N.A.D.
1623	3	N.A.D.		3		3		1	2		3		-		3			3	12.7	-	3	0	N.A.D.
1624	2	N.A.D.		2		2			2		2		-		2			2	12.0	-	2	0	N.A.D.
1625	4	N.A.D.		4		4		1	3		4		-		4			4	13.2	-	4	0	N.A.D.
1626	2	N.A.D.		2		2			2		2		-		2			2	13.0	-	2	0	N.A.D.
1627	4	N.A.D.		4		4		3	1		4		-		4			4	12.5	-	4	0	N.A.D.
1628	4	N.A.D.		4		4			4		3	1f	-		4			4	12.3	-	4	0	N.A.D.
1629	6m	N.A.D.		4		4		2	2		3	1f	-		3	1		4	12.2	-	4	0	N.A.D.

Explanation of symbols follows

EMBRYOTOXICITY STUDY

Examination for skeletal abnormalities

Compound: Octoprox

Dose: 63 mg/kg

Route: oral

Animal: Himalayan rabbit

DAM No. 1/78	No. of fetuses	Head	Cervical vertebrae 0-6	Cervical vertebrae 7	Thoracic vertebrae 0-12	Thoracic vertebrae 13	Sternum (sternebrae) 0-4	Sternum (sternebrae) 5	Sternum (sternebrae) 6	Ribs 0-11	Ribs 12	Ribs 13	Cervical ribs	Lumbar vertebrae 0-5	Lumbar vertebrae 6	Lumbar vertebrae 7	Sacral vertebrae 0-5	Sacral vertebrae 6	Caudal vertebrae $\bar{x}$	Fragm. vertebral centra	Extremities ossification of metacarpal Yes	Extremities ossification of metacarpal No	Remainder of skeleton
1630	4	N.A.D.		4		4		1i	3		2	1f 1g	1c		4			4	13.7	-	4	0	N.A.D.
1631	3	N.A.D.		3		3		3			3		1c		3			3	13.0	-	3	0	N.A.D.
1632	2	N.A.D.		2		2			2		2		-		2			2	12.5	-	2	0	N.A.D.
1633	6	5a	5	1	5	1	5	1		5	1		-	5	1		5	1	13.0	-	1	5	5a
1634	5	N.A.D.		5		5		1	4		5		1c 1d		5			5	13.2	-	5	0	N.A.D.
1635	4	1b		4		4			4		4		-		4			4	12.7	-	4	0	N.A.D.
1636	4	N.A.D.		4		4		2	2		4		-		4			4	13.0 1j	-	4	0	N.A.D.
1637	2	N.A.D.		2		2			2		2		-		2			2	12.5	-	2	0	N.A.D.
1638	4	N.A.D.		4		4		3	1		4		-		4			4	12.2	-	4	0	N.A.D.
1639	4	1a	1	3	1	3	1	2	1	1	3		-	1	3		1	3	12.7	-	3	1	1a
1640	2	N.A.D.		2		2		1	1		2		-		2			2	12.0	-	2	0	N.A.D.
1641	2	N.A.D.		2		2			2		2		-		2			2	13.5 1k	-	2	0	N.A.D.
1642	4	N.A.D.		4		4		1	3		4		-		4			4	13.0	-	4	0	N.A.D.
1643	3	N.A.D.		3		3		2	1		3		-		3			3	12.3	-	3	0	N.A.D.
1644	1	N.A.D.		1		1			1		1		-		1			1	13.0	-	1	0	N.A.D.

Explanation of symbols follows

EMBRYOTOXICITY STUDY OF OCTOPIROX IN HIMALAYAN RABBIT

Explanation of symbols on pp. 25 - 28

(The figure preceding the symbol indicates the number of fetuses)

a Stunted dead fetus; slightly ossified total skeleton

b Protruding vault of skull; slightly ossified nasal and frontal bones; cleft palate

c Short or normally long rib on 7th cervical vertebra, unilaterally

d Short rib on 7th cervical vertebra, bilaterally

e Dysplastic 5th cervical arch

f Short or normally long 13th rib, unilaterally

g Short and/or normally long 13th rib, bilaterally

h Aplastic thoracic vertebra and pair of ribs

i Fused 4th and 5th sternebrae

j Fused 12th and 13th caudal vertebral centers

k Dislocated caudal vertebral centers

m Offspring from premature birth on day 28 of pregnancy; 2 offspring not examined

HOECHST AG PHARMA RESEARCH TOXICOLOGY

STUDY:EMBRYOTOXICITY PREPARATION:OCTOPIROX ANIMAL:RABBIT HIMALAYAN
SEX:FEMALE CESAREAN SECTION ON DAY 29 DOSING FROM DAY 7 - 19 POST COPULATIONEM
ROUTE:ORAL VEHICLE:STARCH MUCILAGE
START OF STUDY:10/23/78 STUDY NO:G2K0246

SURVEY OF BODY AND ORGAN WEIGHTS G IN DAMS

DOSE	BODY WEIGHT			HEART				LIVER				KIDNEYS			
MG/KG	N	X	S	N	X	S		N	X	S		N	X	S	
CONTROL	15	2752	128	15	5.39	0.52	N	15	52.44	5.67	N	15	13.59	1.19	N
16	14	2510	147	14	5.26	0.48	-N	14	52.65	6.68	-N	14	13.87	1.52	-N
32	14	2737	199	14	5.67	0.58	-N	14	54.69	7.00	-N	14	14.53	1.17	-N
63	15	2769	209	15	5.16	0.40	-N	15	53.52	7.33	-N	15	13.43	1.53	-N

DOSE	SPLEEN			
MG/KG	N	X	S	
CONTROL	15	0.59	0.15	N
16	14	0.64	0.12	-N
32	14	0.66	0.15	-N
63	15	0.65	0.15	-N

- = NO DIFFERENCE FROM CONTROL (P>.05)
N = WITHIN NORMAL RANGE

* = SIGNIFICANTLY DIFFERENT FROM CONTROL (P<.05)
A = OUTSIDE NORMAL RANGE

STUDY:EMBRYOTOXICITY PREPARATION:OCTOPIROX ANIMAL:RABBIT HIMALAYAN
SEX:FEMALE CESAREAN SECTION ON DAY 29 DOSING FROM DAY 7 - 19 POST COPULATIONEM
ROUTE:ORAL VEHICLE:STARCH MUCILAGE
START OF STUDY:10/23/78 STUDY NO:G2K0246

STATISTICAL METHODS

PARAMETER	METHOD	PARAMETER	METHOD
FOOD CONSUMPTION :		ORGAN WEIGHTS :	
START	1	HEART	1
DURING DOSING	1	LIVER	1
END	1	KIDNEYS	1
		SPLEEN	2
BODY WEIGHT :			
START	1		
DURING DOSING	1		
END	2		
CESAREAN SECTION PARAMETERS :			
CORPORA LUTEA	3		
IMPLANTATIONS	3		
RESORPTION SITES	3		
DEAD FETUSES	3		
LIVE FETUSES	3		
PARAMETERS OF FETUSES :			
BODY WEIGHT	2		
CROWN-RUMP LENGTH	1		
PLACENTAL WEIGHT	1		
SURVIVAL RATE	4		

0 = NO CALCULATION POSSIBLE
1 = DUNNETT'S SIMULTANEOUS COMPARISON
2 = NEMENYI'S MANY-ONE VERSION OF THE H-TEST
3 = GOODMAN'S SIMULTANEOUS COMPARISON
4 = SIMULTANEOUS COMPARISON WITH CONTROL ACCORDING TO WILCOXON

HOECHST AG PHARMA RESEARCH TOXICOLOGY

STUDY:EMBRYOTOXICITY PREPARATION:OCTOPIROX ANIMAL:RABBIT HIMALAYAN
SEX:FEMALE CESAREAN SECTION ON DAY 29 DOSING FROM DAY 7 - 19 POST COPULATIONEM
ROUTE:ORAL VEHICLE:STARCH MUCILAGE
START OF STUDY:10/23/78 STUDY NO:62K0246

GENERAL VIEW OF ALL CONTROL ANIMALS

FEMALES	NO. OF POSSIBLE VALUES	PARAMETER (-MISSING=AVAILABLE VALUES TO NORMAL RANGE CALCULATION)
PREGNANT	235	
DIED	- 0	
DELIVERED PREMATURELY	- 10	
WITH ABORTION OR ONLY EARLY RES	- 7	
PREGNANT ON DAY 29	218	CORPORA LUTEA RESORPTION SITES,DEAD AND LIVE FETUSES IMPLANTATIONS
WITH ONLY RES	- 4	
WITH ONLY DEAD FETUSES	- 0	
WITH DEAD IMPLANTATIONS	- 0	
LITTERS WITH AT LEAST ONE LIVE FETUS	214	DAM: BODY WEIGHT ADRENALS(-98=116) HEART LIVER FETUSES: BODY WEIGHT SURVIVAL RATE FOOD CONSUMPTION(-106=108) SPLEEN KIDNEYS(-1=213) PLACENTAL WEIGHT CROWN-RUMP LENGTH

STUDY:EMBRYOTOXICITY SPECIES:RABBIT HIMALAYAN
DOSING FROM DAY 7 TO 19 POST COPULATIONEM

WEIGHT DATA IN DAMS ON DAY 0 7 14 20 29 POST COPULATIONEM

NO. OF DAMS GROUP #1 / NORM.RGE #2	DAILY FOOD CONSUMPTION G/100 G BODY WT (108) START	DURING DOSING	END	BODY WEIGHT G (214) START	DURING DOSING	END
6 / 5	1.63 - 4.98	0.91 - 4.65	0.52 - 4.68			
7 / 6	1.59 - 5.07	0.86 - 4.84	0.12 - 4.81			
8 / 7	1.59 - 5.07	0.86 - 4.84	0.12 - 4.81			
10 / 9	1.38 - 5.62	0.52 - 5.44	0.00 - 4.87			
14 / 13				2100 -3210	2072 -3134	2210 -3210
15 / 13				2160 -3120	2208 -3081	2255 -3150

MEAN VALUES IN FETUSES PER DAM AT CESAREAN SECTION

NO. OF DAMS GROUP #1 / NORM.RGE #2	BODY WEIGHT G (214)	CROWN-RUMP LENGTH CM (214)	PLACENTAL WEIGHT G (214)	SURVIVAL RATE % (214)
14 / 13	25.25 -49.70	7.95 -10.67	3.70 - 7.77	50.00 - 100.00
15 / 13	30.04 -49.00	8.15 -10.50	3.85 - 7.43	60.00 - 100.00

A GROUP MARKED WITH #1 DAMS IS CONSIDERED NORMAL, IF AT LEAST #2 DAMS LIE IN RANGE SHOWN.

THE NUMBER IN BRACKETS INDICATES THE RESPECTIVE NUMBER OF CONTROL ANIMALS.

STUDY:EMBRYOTOXICITY SPECIES:RABBIT HIMALAYAN
DOSING FROM DAY 7 TO 19 POST COPULATIONEM

CESAREAN SECTION PARAMETERS IN DAMS

IN GROUP #1	NUMBER OF DAMS WITH CORPORA LUTEA (218)	WITH IMPLANTATIONS (218)	IMPLANTATIONS (218) #1	FETUSES LIVE	FETUSES DEAD	RESORPTION SITES
14	4 - 12	6 - 13	96	76 - 90	0 - 6	2 - 14
15	5 - 13	7 - 14	99	79 - 93	0 - 7	3 - 15
			93	74 - 88	0 - 6	2 - 14
			102	81 - 96	0 - 7	3 - 15

A GROUP OF #1 DAMS IS CONSIDERED NORMAL, IF THE NOS OF DAMS WITH MAX 7 CORP LUT OR 7 IMPLANTATIONS LIE WITHIN THE RANGE SHOWN.

A GROUP OF #1 IMPLANTATIONS IS CONSIDERED NORMAL, IF THE NOS OF THE 3 PARAMETERS IN THE GROUP LIE WITHIN THE RANGES SHOWN.

THE DOSE GROUPS ARE NOT COMPARED, IF THE GROUP LIES OUTSIDE THE NORMAL RANGE

THE NUMBER IN BRACKETS INDICATES THE RESPECTIVE NUMBER OF CONTROL ANIMALS.

STUDY:EMBRYOTOXICITY SPECIES:RABBIT HIMALAYAN
DOSING FROM DAY 7 TO 19 POST COPULATIONEM

ORGAN WEIGHTS G IN DAMS - AUTOPSY ON DAY 29 POST COPULATIONEM

NO. GROUP	DAMS /NORM.RGE #1	#2	HEART (214)	LIVER (214)	KIDNEYS (213)	SPLEEN (214)
14	/	13	3.94 - 7.46	38.86 - 84.51	10.09 - 18.05	0.37 - 1.35
15	/	13	4.39 - 6.85	41.13 - 77.82	11.03 - 17.38	0.38 - 1.13

A GROUP MARKED WITH #1 DAMS IS CONSIDERED NORMAL,IF AT LEAST #2 DAMS LIE IN RANGE SHOWN.

THE NUMBER IN BRACKETS INDICATES THE RESPECTIVE NUMBER OF CONTROL ANIMALS.

Composition of the food (ERKA Z 6000)

Crude nutrients

Protein	16.49 %
Fat	3.02 %
Fiber	15.47 %
Ash	7.83 %
Hardness	11.36 kg
Dry basis	88.60 %

Vitamins (in 1000 g diet)

A	(IU)	12000
Carotene(A)	(IU)	ca. 15000
D_3	(IU)	1260
E	(mg)	92.846
B_1	(mg)	4.333
B_2	(mg)	6.646
B_6	(mg)	10.514
B_{12}	(µg)	13.981
Nic. acid	(mg)	76.338
Pantoth. acid	(mg)	20.268
Folic acid	(mg)	2.097
Choline	(mg)	1082.0
Biotin	(µg)	115

Amino acids

Arginine	0.879 %
Glycine	0.756 %
Histidine	0.325 %
Lysine	0.760 %
Methionine	0.245 %
Cystine	0.262 %
M. + C.	0.507 %
Threonine	0.615 %
Tryptophan	0.239 %

Minerals and trace elements

Calcium	1.627 %
Phosphorus	0.602 %
Salt	0.683 %
Potassium	1.280 %
Magnesium	0.285 %
Manganese	0.0043 %
Iodine	0.0222 %
Iron	0.0416 %
Copper	0.0010 %
Zinc	ca. 0.00051 %

Hoechst Aktiengesellschaft
Pharma Research
Quality Assurance (GLP)

Title : An oral embryotoxicity study of Octopirox in rabbits (report No. 603/79)

Date : October 11, 1979

Study No.: G2K0246

This study was periodically inspected and properly signed records of these inspections submitted to testing facility management and the study director as shown below:

Inspection	Report
October 26, 1978	----------
December 14, 1978	December 14, 1978
October 25, 1979	October 25, 1979

S. J. Harston
Quality Assurance

Vorsitzender des Aufsichtsrats: Karl Winnacker · Vorstand: Rolf Sammet, Vorsitzender, Kurt Lanz, stellv. Vorsitzender, Erhard Bouillon, Rudolf Frank, Enrique Hartung, Wolfgang Hilger, Willi Hoerkens, Josef Nowotny, Wolfgang von Reinitz, Hans Reinides, Jürgen Schaafhausen, Hans Schlechter, Klaus Weissermel, stellv. Martin Prühauf · Sitz der Gesellschaft: Frankfurt am Main · Handelsregister: Frankfurt am Main Abt. B Nr. 4300