C.3 Reproductive Toxicology

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Conducted by : Boehringer Ingelheim KG
Department of Experimental Pathology and Toxicology
D-6507 Ingelheim am Rhein
West Germany

These studies complied with GLP

C.3.a. Segment I in Rats: Fertility and Reproduction

Document #(s): BI Document U89-0232
Upjohn TR 7219-94-077

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Sponsor Volume: 1.42

Summary:

Pramipexole was administered by gavage at doses of 0, 0.1, 0.5 and 2.5 mg/kg/day to Wistar (Chbb:THOM) rats (24/sex/dose). Males were treated for 70 days prior to mating, and sacrificed after mating. Females were treated for 14 days prior to mating. One half of the females were treated through gestation, and sacrificed on day 22 for delivery of pups by Caesarean section. The remaining females littered spontaneously and drug treatment was continued through the weaning period (21 days).

Overt drug-related changes were restlessness and agitation with the middle and high doses, and decreased body weight gain and food intake at the high dose. No reproductive toxicities (abnormalities in mating, pregnancy or pup development) were apparent in animals of the low-dose group, or the mid-dose animals (dams and pups) delivered by Caesarean section. Significant toxicities were evident in the high-dose treatment group. Irregular estrus (prolongation by 1-2 days) occurred in about one-half of the HDF; hence, a longer mating period was required for successful insemination. In addition, the numbers of corpora lutea, implantations, pregnant females and females that successfully delivered were markedly reduced. Teratogenic effects of pramipexole were not evident, but one case of micrognathia inferior occurred in an MD pup. The teratogenicity data are limited by the low number of evaluable pups. Body weight development was impaired in pups from the mid- and high dose dams, but statistical evaluation of the high dose pup data was not possible due to the low number of reared pups. The sponsor suggests this impairment may have been due to drug-induced CNS stimulation in the dams resulting in reduced suckling opportunities. An alternative possibility is that inhibition of prolactin secretion by PPX reduced milk production in dams. Other developmental parameters, including fertility, were not affected by PPX. Histopathological findings in F_0 animals were prostate edema in one male subject from each dosage group, and hydronephrosis in one MD and one HD dam. The analysis of the testes may be considered inadequate since tissue fixation was in formalin rather than Bouin's solution. Plasma concentrations were not measured in this study. Thus, prampipexole produces significant reproductive toxicity, most evident as a reduction in successful pregnancies at a dose of 2.5 mg/kg. In view of the established role of prolactin in the

maintenance of pregnancy in the rat, and the probability that this dopamine agonist inhibits prolactin secretion, it is likely that the infertility is due to effects in the dam. However, additional studies are necessary to determine the source of infertility.

Methods:

Dosages: 0.1, 0.5, 2.5 mg/kg/day (Drug Lot: Batch III; prepared in distilled water)

Low dose is five times the expected human dose (at the time of study initiation). The high dose was selected as the highest tolerable dose based on a range-finding study.

Route of Administration: oral (gavage)

Species/Number: 96 males and 96 nulliparous females

Mean initial weights/age:

males:	218 g / 8 weeks	APPEARS THIS WAY ON ORIGINAL
females:	209 g / 11 weeks	

Parameters monitored/Intervals:

Clinical	-	daily
Body weight	-	weekly in males; daily in females
Food consumption	-	weekly
At Termination	-	APPEARS THIS WAY ON ORIGINAL

Males: Testes and epididymis were weighed, fixed in 7.5% formalin, and stored.

Females: Gross pathology, numbers of fetuses (viable and dead), corpora lutea, and resorptions. Non-pregnant females were excluded from mean calculations.

Fetuses: (C-section group) Live/dead, sex, external, skeletal (2/3 of subjects), and visceral (1/3 of subjects) abnormalities.

Pups: (rearing group) Live/dead, body weight, sex, gross abnormalities, functional/maturational parameters (erection of pinnae, fur growth, eye opening, etc.). At weaning, four pups (2 male, 2 female) were retained for additional developmental tests (simming, Preyer reflex, pupillary reflex, water T-maze), and fertility testing at 10 weeks. All pups were examined for pathological changes.

Statistics

Statistical comparisons were made by Bartlett test, one-way ANOVA, Newman-Keuls or Dunnett's test for multiple comparisons, and Chi-square and Fisher's exact test.

Results:

Effects in Males:

Mortality: none

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Clinical Signs:

Dose-dependent increases in the severity and duration of restlessness and agitation were evident in MD and HD males.

Body Weight Gain:

Significantly decreased in the HD groups during weeks 1-10 (Fig. C.3.a.1).

Food Intake:

Significantly decreased in the HD groups during week 1, and increased during weeks 2-3 (Fig. C.3.a.2).

Copulation:

One control and one MD male did not copulate.

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Necropsy:

Prostate edema occurred in one male from each dose group (LD, MD, HD). One control male had unilateral testicular hypoplasia, but there were no significant differences in testicular weights among treatment groups.

Effects in Females:

Mortality: none

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Clinical Signs:

Dose-dependent increases in the severity and duration of restlessness were evident MD and HD during the entire treatment period.

Body Weight Gain:

Mean body weight was significantly reduced in the HD group during week 1 of treatment. After mating, the only significant effect on body weight was a slight decrease in the HD C-section group (Fig. C.3.a.3).

Food Intake:

Decreased in the HD group during week 1, and in the LD group during week 2.

Estrous Cycle:

A dose-dependent increase in estrous cycle irregularities was evident (2 LDF, 3 MDF, 13 HDF). For 4 HD females, two estrous cycles were required for successful insemination (Tab. C.3.a.1).

Gestation (Tab. C.3.a.2):

C-section group: Of 12 rats per dose group, 1 MD and 10 HD animals were not pregnant. Body weight and food consumption did not differ among groups.

Spontaneous delivery group: Seven of 12 dams in the HD group did not become pregnant. Body weight did not differ significantly among groups . Food consumption was significantly reduced throughout lactation in the HD group, and during week 1 of lactation in the LD group.

Necropsy: One MD and 1 HD dam had unilateral hydronephrosis.

Effects on fetuses and pups:

C-section group: Only 2 of 12 HD dams were pregnant, and only one had viable fetuses. There were no statistical variations among control, LD and MD litters; the HD group was not included in the analyses because of the low survivor number. The number of implantations in the HD group is clearly lower than in other groups. There were no dose-related trends in the incidence of malformations or skeletal and visceral variations, although one case of micrognathia inferior was found in an MD pup (Tables C.3.a.3-5).

Spontaneous delivery group: Significant reductions in weight were recorded in HD pups at birth, day 4 and day 21, and in MD pups at day 21. Body weight gain from days 1-4 and days 4-21 was also significantly reduced in MD and HD pups (Tables C.3.a.6-7; Fig.C.3.a.4).

The only other notable difference in tests of pup maturation and behavior was a slight (insignificant) delay in eye-opening in MD and HD pups. No drug-related pathological changes were identified in pups (Table C.3.a.8). In fertility studies of the F1 generation, no overt fertility impairments were apparent. Body weights of the F_1 MD and HD dams were reduced during their gestational period, but body weight gain during gestation did not differ among groups of F_1 offspring (Fig. C.3.a.5).

C.3.a.1

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Fig. C.3.a.1

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Males- Bodyweight

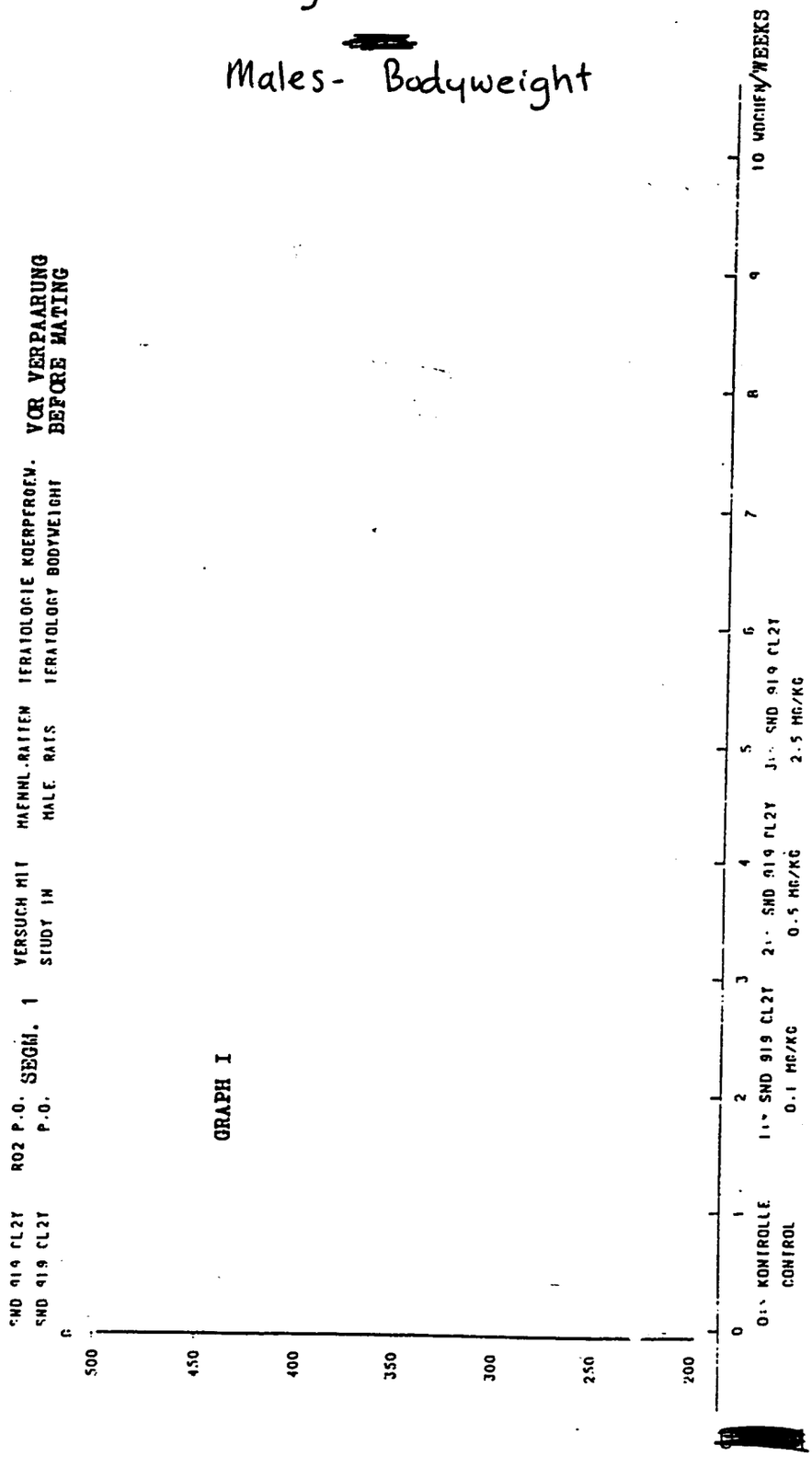

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Figure C.3.a.2.

Males - Food Consumption

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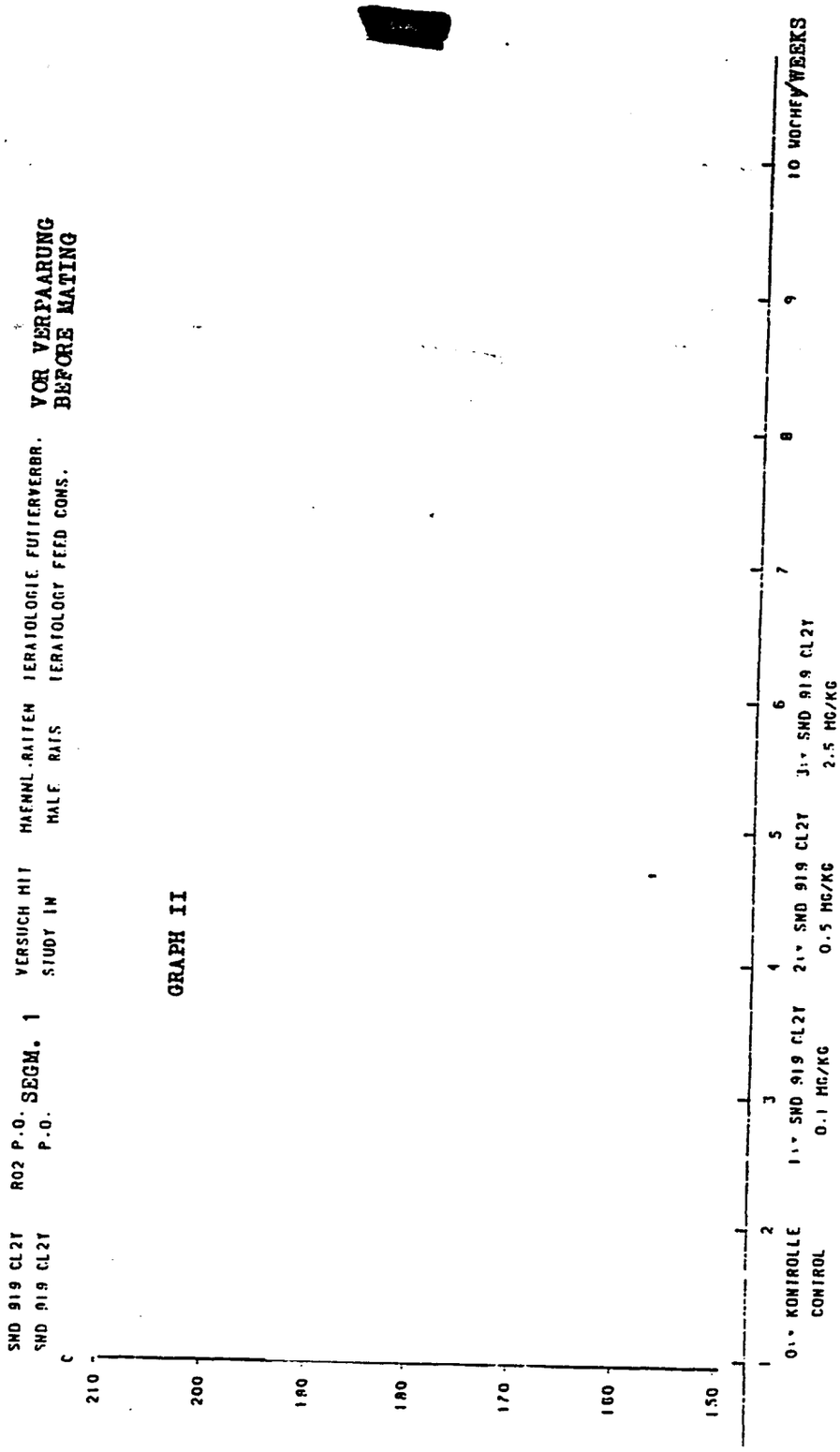

Fig. C.3.a.3

Females - Bodyweight

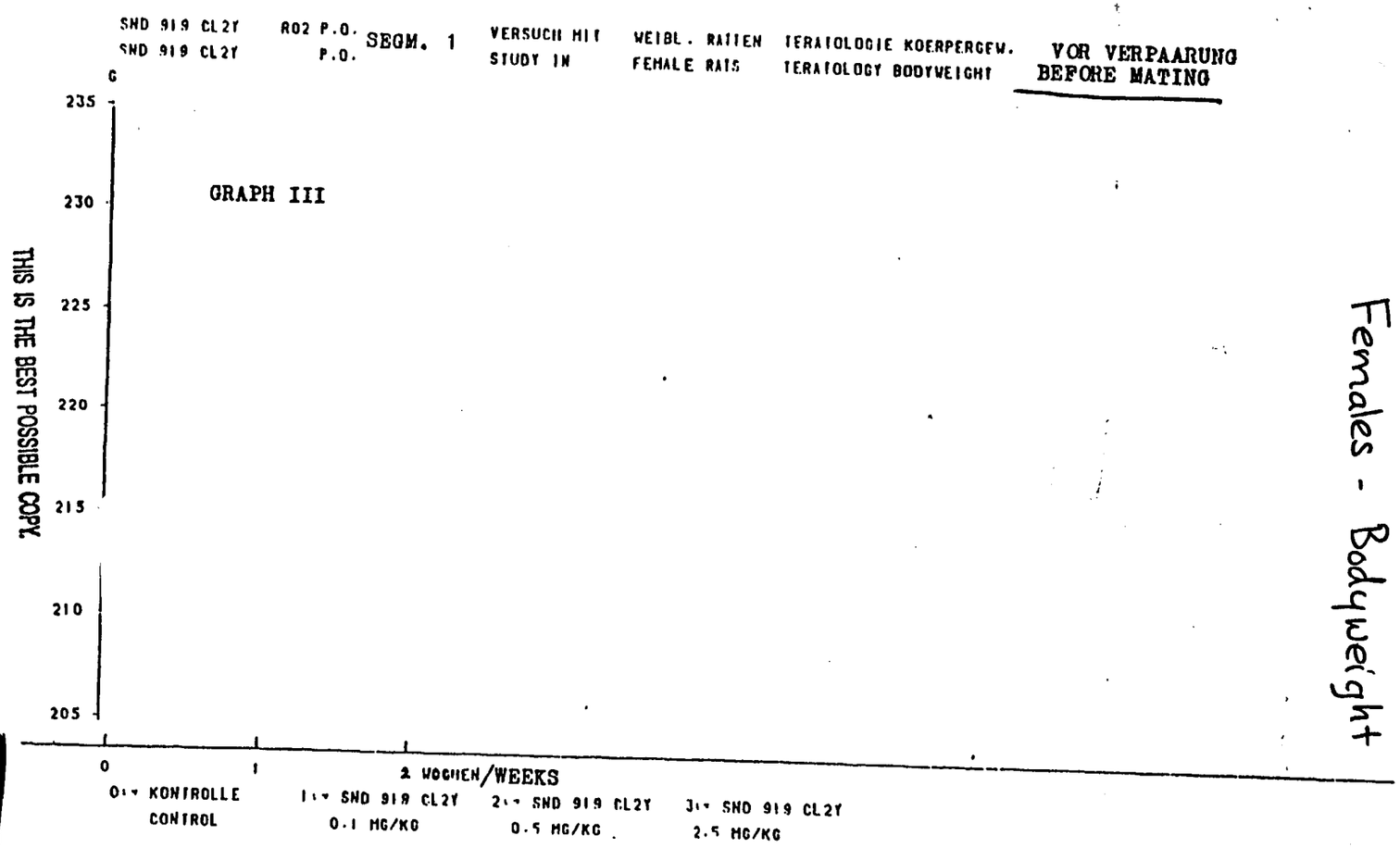

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Fig. C.3.a.3. (cont.)

Females - Bodyweight

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SEGM. 1 VERSUCH MIT WEIBL. RATTEN TERATOLOGIE KOERPERGEW. WAEHREND DER GRAVIDITAET
STUDY IN FEMALE RATS TERATOLOGY BODYWEIGHT DURING GESTATION PERIOD

KAISERSCHNITT-GRUPPE / CAESAREAN SECTION GROUP

GRAPH IV

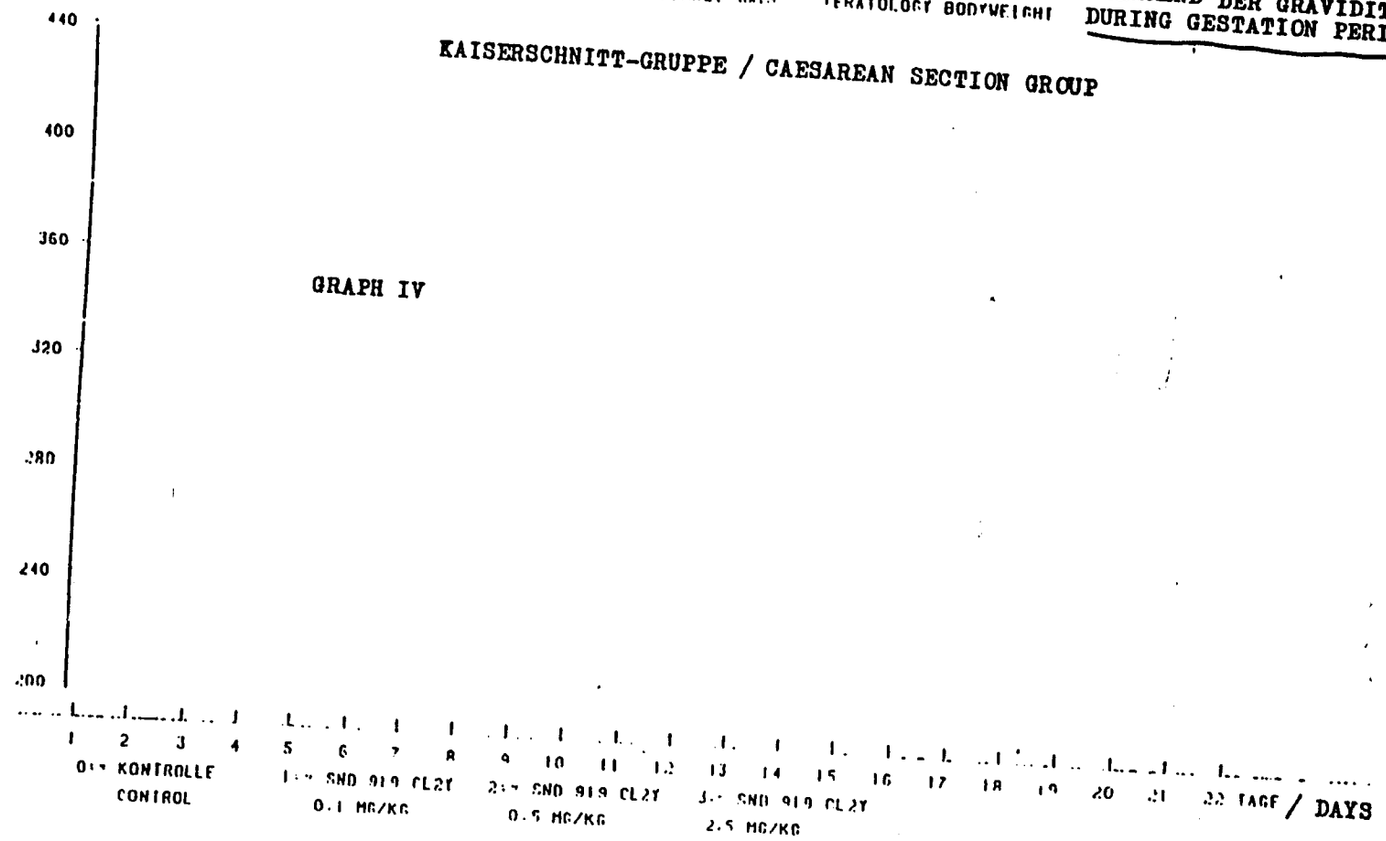

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Fig. C.3.a.3.(cont.)

Females - Bodyweight

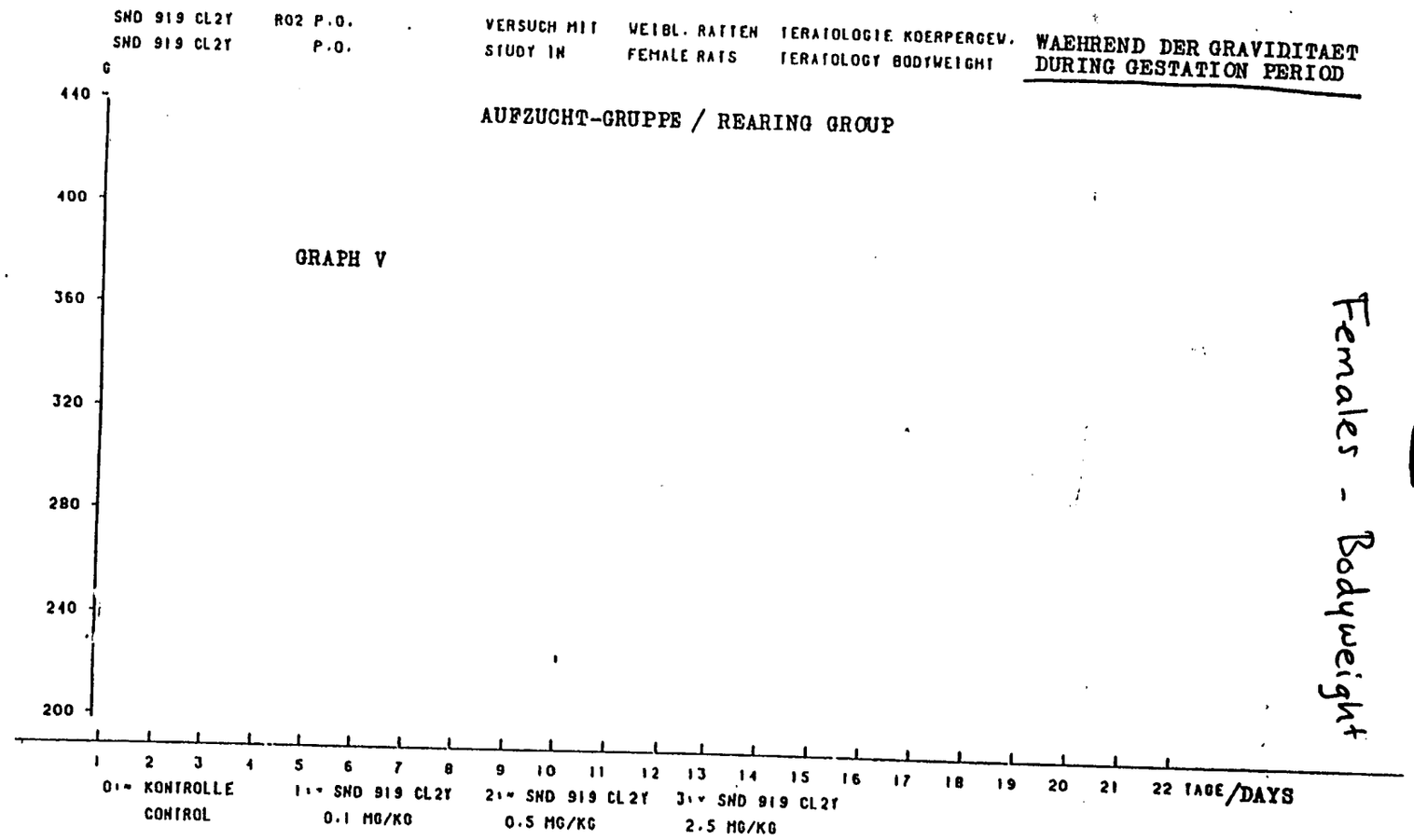

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Fig. C.3.a.3. (cont.)

Females- Bodyweight

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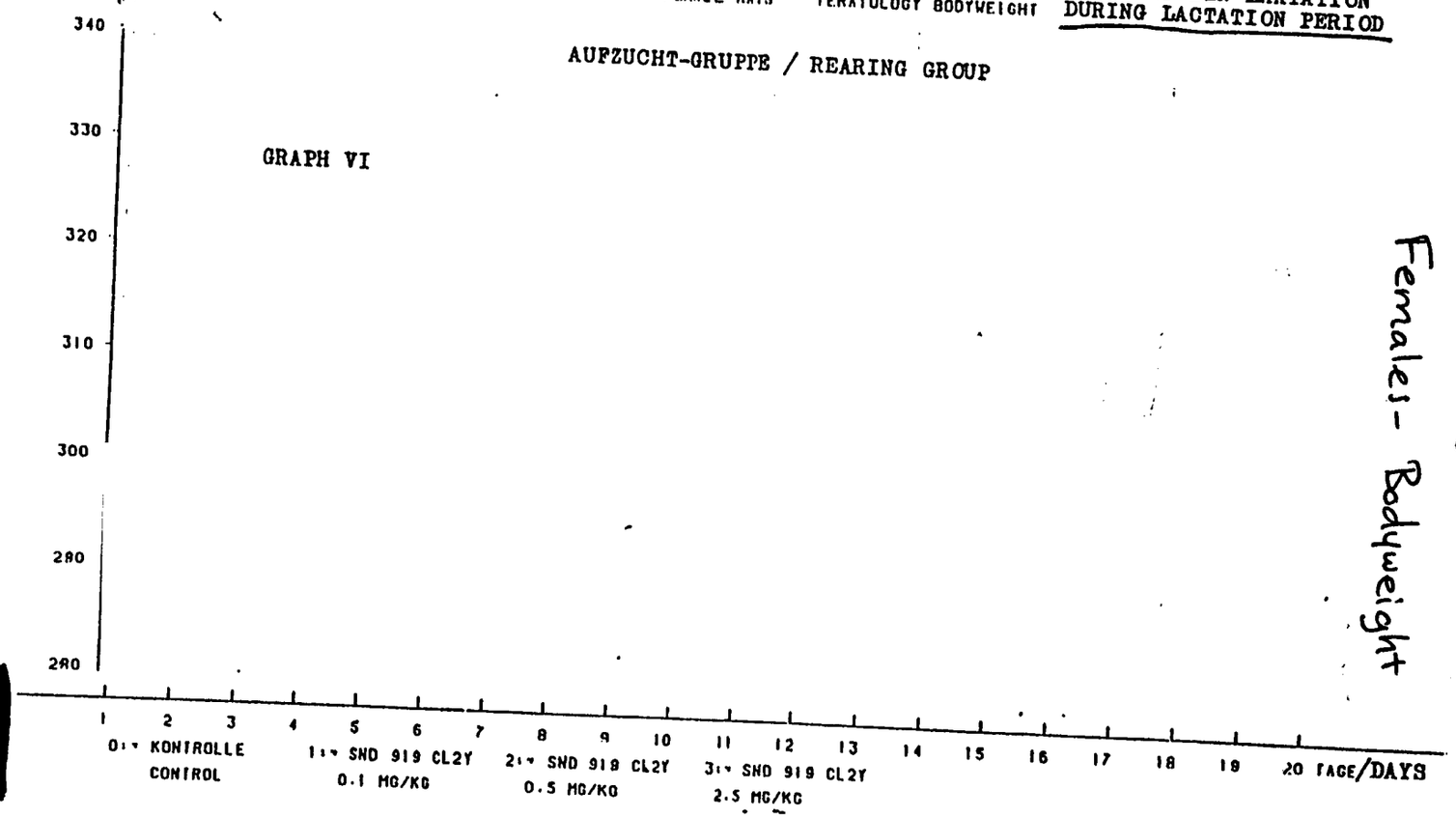
SND 919 CL2Y P.O. STUDY IN FEMALE RATS TERATOLOGY BODYWEIGHT DURING LACTATION PERIOD

AUFZUCHT-GRUPPE / REARING GROUP

GRAPH VI



Tab. C.3.a.1

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RATTEN/RATS

DAUER DES OESTRUSZYKLUS WÄHREND DER APPLIKATIONSPERIODE
LENGTH OF ESTROUS CYCLE DURING ADMINISTRATION PERIOD

DOSIS DOSE	ANZAHL TIERE NO. OF ANIM.	REGELMÄSSIG (4 TAGE) REGULAR (4 DAYS)	UNREGELMÄSSIG / IRREGULAR		
			<4 DAYS	>4 DAYS	<AND >4 DAYS
CONTROL	24	24	0	0	0
0.1 MG/KG	24	22	0	2	0
0.5 MG/KG	24	21	0	3	0
2.5 MG/KG	24	11	0	12	1

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SND 919 CL 2 Y

Tab. C.3.a.2.

RATTEN/RATS

VERPAARUNGSERFOLG / MATING PERFORMANCE

GRUPPE GROUP	ANZAHL DER RATTEN MIT POS. ABSTRICH "n" - TAGE NACH DER PAARUNG / NO. OF RATS WITH POSITIVE SMEARS AT "n" - DAYS AFTER PAIRING													ANZAHL TRAECHTIGER TIERE / NO. OF PREGNANT ANIMALS		
	n=1	2	3	4	5	6	7	8	9	10	11	12	GESAMT TOTAL	TÖTUNG 22. TAG SACRIFICED AT DAY 22	TIERE DIE WERFEN ALLOWED TO PRODUCE	GESAMT TOTAL
KONTROLLE	1	6	7	9									23	12	11	23
0.1 MG/KG	8	6	4	6									24	12	12	24
0.5 MG/KG	4	7	8	4									23	11	11	22
2.5 MG/KG	7	6	5	2	2		1		1				24	2	5	7

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Tab. [redacted]

BOEHRINGER INGELHEIM KG REPRODUCTION TOXICOLOGY

SUBST./COMP. : SND 919 CL2 Y VERS.NR./STUDY NO. : R02
TIERART/SPEC. : RATTEN / RATS SEGM. 1

	WURFDATEN / LITTER DATA SUMMENWERTE / SUM VALUES		KAISERSCHNITT-GRUPPE CAESAREAN SECTION GROUP	
	KONTROLLE CONTROL	0.1 MG/KG	0.5 MG/KG	2.5 MG/KG
GESAMTZAHL DER TIERE TOTAL NUMBER OF ANIMALS	12	12	12	12
TODESFAELLE MATERNAL MORTALITY	0	0	0	0
TOTALRESORPTIONEN TOTAL RESORPTIONS	0	0	0	~~0~~ 1
SPONTANWUERFE NATURAL DELIVERIES	0	0	0	0
TIERE MIT LEB. FETEN ANIM. WITH VIABLE FET.	12	12	11	~~2~~ 1
GELBKOERPER CORPORA LUTEA	191	186	171	34
IMPLANTATIONEN IMPLANTATIONS	185	172	157	24
LEBENDE FETEN VIABLE FETUSES	174	162	146	10
MAENNLICH IN % MALE IN %	47	48	51	50
WEIBLICH IN % FEMALE IN %	53	52	49	50
TOTE FETEN DEAD FETUSES	0	0	0	0
RESORPTIONEN RESORPTIONS	11	10	11	~~14~~ 3
FRUEH IN % EARLY IN %	64	70	55	93
SPAET IN % LATE IN %	36	30	45	7
MISSBILDUNGEN MALFORMATIONS	1	0	1	0
VARIATIONEN VARIATIONS	15	15	8	0

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SUBST./COMP. : SND 919 CL2Y
TIERART/SPEC. : RATTEN / RATS

VERS.NR./STUDY NO. : R02
SEGM. 1

WURFDATEN / LITTER DATA
MITTELWERTE / MEAN VALUES

KAISERSCHNITT-GRUPPE
CAESAREAN SECTION GROUP

		KONTROLLE CONTROL	0.1 MG/KG	0.5 MG/KG	2.5 MG/KG
GEWICHT / FET (G) WEIGHT / FETUS (G)	MW	5.01	5.25	5.26	5.25
	SD	0.19	0.22	0.30	0.00
PLAZ.GEW. / FET (G) PLAC. WEIGHT/ FETUS (G)	MW	0.44	0.41	0.40	0.44
	SD	0.08	0.02	0.04	0.00
CORPORA LUTEA / MUTTERT. CORPORA LUTEA / DAM	MW	15.9	15.5	15.5	23.0
	SD	1.6	1.6	1.4	0.0
IMPLANTATIONEN / MUTTERT. IMPLANTATIONS / DAM	MW	15.4	14.3	14.3	13.0
	SD	1.7	1.9	1.6	0.0
LEBENDE FETEN / MUTTERT. VIABLE FETUSES / DAM	MW	14.5	13.5	13.3	10.0
	SD	1.7	1.7	1.7	0.0
TOTE FETEN / MUTTERT. DEAD FETUSES / DAM	MW	0.0	0.0	0.0	0.0
	SD	0.0	0.0	0.0	0.0
RESORPTIONEN / MUTTERT. RESORPTIONS / DAM	MW	0.9	0.8	1.0	3.0
	SD	1.1	0.9	0.8	0.0
MISSBILDUNGEN / MUTTERT. MALFORMATIONS / DAM	MW	0.1	0.0	0.1	0.0
	SD	0.3	0.0	0.3	0.0
VARIATIONEN / MUTTERT. VARIATIONS / DAM	MW	1.3	1.3	0.7	0.0
	SD	1.5	1.5	1.3	0.0
LEB. FETEN IN % IMPL. VIABLE FET. IN % IMPL.	MW	97.2	95.9	94.9	76.9
	SD	3.4	2.8	2.3	0.0
RESORPTIONEN IN % IMPL. RESORPTIONS IN % IMPL.	MW	2.8	3.1	5.1	23.1
	SD	3.4	2.8	2.3	0.0
PRAEIMPLANTAT.-VERLUST PRE IMPLANTAT. LOSS %	MW	1.6	3.7	4.1	43.5
	SD	1.8	4.4	4.6	0.0
POSTIMPLANTAT.-VERLUST POST IMPLANTAT. LOSS %	MW	2.8	3.1	5.1	23.1
	SD	3.4	2.8	2.3	0.0
MISSB. IN % LEB. FET. MALFORM. IN % VIAB. FET.	MW	0.1	0.0	0.1	0.0
	SD	0.6	0.0	0.7	0.0
VARIAT. IN % LEB. FET. VARIAT. IN % VIAB. FET.	MW	10.7	9.8	3.7	0.0
	SD	10.4	10.0	8.8	0.0

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CALCULATIONS OF PERCENTAGES ARE ARCSINE-TRANSFORMATIONS

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Study No.: R 02

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Tab. C.3.a.5.

RATTEN/RATS

BEFUNDE AN FETEN FINDINGS IN FETUSES	KAISERSCHNITT-GRUPPE CAESAREAN SECTION GROUP			
	Contr.	0.1 MG/KG	0.5 MG/KG	2.5 MG/KG
TOTAL NO. OF FETUSES EXAMINED	174	162	146	10
FOR SKELETAL DIAGNOSIS	115	108	105	7
FOR VISCERAL DIAGNOSIS	59	54	41	3
EXTERNAL				
POLYDACTYLIA RIGHT FOREPAW	1	0	0	0
MICROGNATHIA INFERIOR	0	0	1	0
SKELETAL				
RUDIMENTARY 13TH RIB	7	9	4	0
ADDITIONAL 14TH RIB	2	1	0	0
GENERAL INCOMPLETENESS OF OSSIFICATION	0	0	1	0
VISCERAL				
DILATATION OF RENAL PELVIS (UNI- OR BILATERAL)	6	5	3	0
RUNTS	0	0	1	0
ADDITIONAL FINDINGS IN STERNEBRAE				
POORLY OSSIFIED STERNEBRA V	8	4	3	0
POORLY OSSIFIED STERNEBRAE II, IV, V	1	0	0	0
POORLY OSSIFIED STERNEBRAE I, II, V	0	1	0	0
POORLY OSSIFIED STERNEBRAE II, III, IV, V	0	0	1	0

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Tab. C.3.a.b.

- BOEHRINGER INGELHEIM KG -

VERS.NR./STUDY.NO.: R02 SEGM. 1

SND 919CL2Y

RATTEN/RATS

WURFDATEN / LITTER DATA
SUMMENWERTE / SUM VALUES

AUFZUCHT-GRUPPE
REARING GROUP

	KONTR. /CONTR.	0.1 MG/KG	0.5 MG/KG	2.5 MG/KG
GESAMTZAHL TIERE TOTAL NUMBER ANIMALS	11	12	11	12
TODESFAELLE MATERNAL MORTALITY	0	0	0	0
FEHLWUERFE ABORTIONS	0	0	0	0
TRAECHTIGE TIERE PREGNANT ANIMALS	11	12	11	5
TOTE JUNGTIERE STILLBIRTHS	1	0	1	0
JUNGTIERE 1. TAG VIABLE PUPS DAY 1	158	160	157	75
MAENNLICH IN % MALE IN %	51.27	46.25	51.59	48.00
WEIBLICH IN % FEMALE IN %	48.73	53.75	48.41	52.00
JUNGTIERE 4. TAG VIABLE PUPS DAY 4	156	157	156	75
JUNGTIERE 4*. TAG VIABLE PUPS DAY 4*	88	96	88	40
JUNGTIERE 7. TAG VIABLE PUPS DAY 7	88	96	88	40
JUNGTIERE 14. TAG VIABLE PUPS DAY 14	88	96	88	40
JUNGTIERE 21. TAG VIABLE PUPS DAY 21	88	96	88	40
VERENDETE JUNGTIERE MORT. IN PUPS 1 - 4	2	3	1	0
VERENDETE JUNGTIERE MORT. IN PUPS 4* -21	0	0	0	0
MISSBILDUNGEN MALFORMATIONS	0	1	0	0
VARIATIONEN VARIATIONS	0	0	0	0

* NACH WURFREDUZIERUNG/AFTER LITTER REDUCTION

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- BOEHRINGER INGELHEIM KG -

SND 919CL2Y VERS.NR./STUDY.NO.: R02 SEGM. 1

WURFDATEN / LITTER-DATA
MITTELWERTE / MEAN-VALUES

RATTEN/RATS
AUFZUCHT-GRUPPE
REARING GROUP

		KONTR. /CONTR.	0.1 MG/KG	0.5 MG/KG	2.5 MG/KG
TRAGEZEIT DER MUTTERTIERE	MW	22.00	22.00	22.00	22.00
GESTATION PERIOD OF DAMS	SD	0.00	0.00	0.00	0.00
ANZ. TIERE / NUMB. OF ANIM.	N	11.00	12.00	11.00	5.00
GEWICHT/JUNGTIER (G) TAG 1	MW	6.12	6.05	6.04	(*) 5.77
WEIGHT/PUP AT (G) DAY 1	SD	0.18	0.30	0.30	0.19
GEWICHT/JUNGTIER (G) TAG 4	MW	7.74	7.72	7.42	** 6.62
WEIGHT/PUP (G) DAY 4	SD	0.26	0.39	0.75	0.35
GEWICHT/JUNGTIER (G) TAG 4*	MW	7.90	7.91	7.57	** 6.90
WEIGHT/PUP (G) DAY 4*	SD	0.26	0.30	0.75	0.33
GEWICHT/JUNGTIER (G) TAG 21	MW	42.63	40.59	*** 36.60	*** 20.91
WEIGHT/PUP (G) DAY 21	SD	2.18	3.15	2.62	5.14
GEWICHTSZUN. (G) TAG 1-4	MW	1.62	1.61	** 1.28	*** 0.84
BODYW. INCR. (G) DAY 1-4	SD	0.36	0.47	0.51	0.38
GEWICHTSZUN. (G) TAG 4*-21	MW	34.72	32.68	** 29.03	*** 14.01
BODYW. INCR. (G) DAY 4*-21	SD	2.67	4.00	2.48	4.49
LEB.JUNGT./MUTTERT. TAG 1	MW	14.36	13.33	14.27	15.00
VIABLE PUPS/ DAM DAY 1	SD	1.03	2.27	3.04	1.41
TOTE JUNGT./MUTTERT. TAG 1	MW	0.09	0.00	0.09	0.00
DEAD PUPS / DAM DAY 1	SD	0.30	0.00	0.30	0.00
LEB.JUNGT./MUTTERT. TAG 4	MW	14.18	13.08	14.18	15.00
VIABLE PUPS/ DAM DAY 4	SD	0.98	2.23	3.03	1.41
LEB.JUNGT./MUTTERT. TAG 4*	MW	8.00	8.00	8.00	8.00
VIABLE PUPS/ DAM DAY 4*	SD	0.00	0.00	0.00	0.00
LEB.JUNGT./MUTTERT. TAG 21	MW	8.00	8.00	8.00	8.00
VIABLE PUPS/ DAM DAY 21	SD	0.00	0.00	0.00	0.00
JUNGTIERVER. % TAG 1-4	MW	1.23	1.80	0.61	0.00
PUPS LOSS % DAY 1-4	SD	2.78	3.28	2.01	0.00
JUNGTIERVERL. % TAG 4*-21	MW	0.00	0.00	0.00	0.00
PUPS LOSS % DAY 4*-21	SD	0.00	0.00	0.00	0.00
MISSBILDUNGEN / MUTTERTIER	MW	0.00	0.08	0.00	0.00
MALFORMATIONS / DAM	SD	0.00	0.29	0.00	0.00
VARIATIONEN / MUTTERTIER	MW	0.00	0.00	0.00	0.00
VARIATIONS / DAM	SD	0.00	0.00	0.00	0.00
MISSB. % LEB. JUNGT./TAG 1	MW	0.00	0.64	0.00	0.00
MALF. % VIAB. PUPS / DAY 1	SD	0.00	2.22	0.00	0.00
VARIAT. % LEB. JUNGT./TAG 1	MW	0.00	0.00	0.00	0.00
VARIAT. % VIAB. PUPS/ DAY 1	SD	0.00	0.00	0.00	0.00

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** = p < 0.01
*** = p < 0.001

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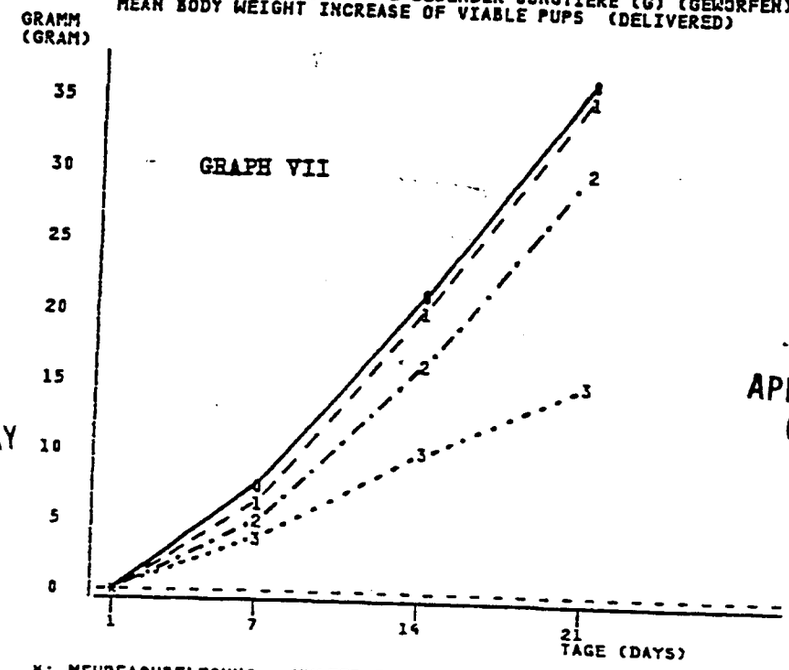
CALCULATIONS OF PERCENTAGES ARE ARCSINE-TRANSFORMATIONS
* NACH WURFREDUZIERUNG/AFTER LITTER REDUCTION

TR No.: 7219-94-077 .Fig. C.3.a.4.

BOEHRINGER INGELHEIM KG REPRODUKTIONSTOXIKOLOGIE

SUBST./COMP. : SND 919 CL2Y TIERART/SPEC. : RATTEN / RATS
VERS.NR./STUDY NO. : R02 SEGM. 1

MITTLERE GEWICHTSZUNAHME LEBENDER JUNGTIERE (G) (GEWORFEN)
MEAN BODY WEIGHT INCREASE OF VIABLE PUPS (DELIVERED)



X: MEHRFACHBELEGUNG - MULTIPLE POINTS
0:KONTR -CONTR 1: 0.1 MG/KG 2: 0.5 MG/KG 3: 2.5 MG/KG

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Study No.: R 02

SND 919 CL 2 Y

Tab. C.3.a.8.

RATTEN/RATS

SEGM. 1

BEOBACHTUNGEN DER F_1-GENERATION DER GRUPPE DER SPONTANGEBURTEN

OBSERVATIONS OF F_1-OFFSPRING IN SPONTANEOUS DELIVERY GROUP

63

ERGEBNISSE IN PROZENT / RESULTS IN PER CENT

DOSIS / DOSE	AUSGEWERTETE WÜRFE / EVALUATED LITTERS	AUFSTELLEN DER OHREN / ERECTION OF PINNAE		FELLWACHSTUM / FUR GROWTH		LAUFEN MIT ANGEHOBENEM BAUCH / RUNNING WITH RAISED VENTER		DURCHBRECHEN DER OBEREN SCHNEIDEZÄHNE / ERUPTION OF MAXILLARY INCISORS		AUGENÖFFNUNG / EYE OPENING		
		TAG / DAY 4	5	TAG / DAY 6	7	TAG / DAY 12	13	TAG / DAY 12	13	TAG / DAY 15	16	17
KONTROLLE/ CONTROL	11	3.4	93.2	-	100.0	100.0	100.0	100.0	100.0	28.4	80.7	100.0
0.1 MG/KG	12	3.1	95.8	-	100.0	100.0	100.0	100.0	100.0	17.7	74.0	98.0
0.5 MG/KG	11	9.1	98.9	-	100.0	100.0	100.0	100.0	100.0	2.3	67.0	100.0
2.5 MG/KG	5	2.5	100.0	-	100.0	100.0	100.0	100.0	100.0	10.0	57.5	100.0

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Fig. C.3.a.5.

TR No.: 7219-94-077

BOEHRINGER INGELHEIM KG REPRODUKTIONSTOXIKOLOGIE

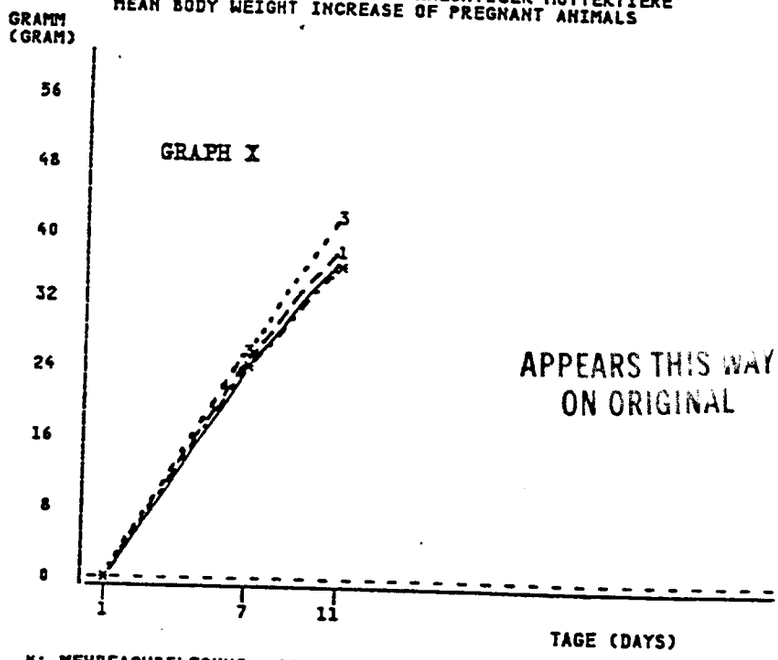
SUBST./COMP. : SHD 919CL2Y TIERART/SPEC. : RATTEN / RATS
VERS.NR./STUDY NO. : R03 SEGM. 1

KOERPERGEWICHT TRAECHTIGER MUTTERTIERE (G) (TAG 1, 7, 11)
BODY WEIGHT OF PREGNANT ANIMALS (G)(DAYS 1, 7, 11) F_1-GENERATION
MITTELWERTE / MEAN VALUES

		N	1	7	11
KONTROLLE CONTROL	MW	10	238.2	261.8	274.4
	SD		13.0	12.1	9.3
0.1 MG/KG	MW	11	228.5	252.8	267.4
	SD		12.8	18.9	24.2
0.5 MG/KG	MW	11	216.8*	240.8*	253.1(*)
	SD		17.1	19.1	20.4
2.5 MG/KG	MW	4	196.8***	223.3**	237.8*
	SD		25.9	27.0	36.6

* $p < 0.05$
** $p < 0.01$
*** $p < 0.001$

MITTLERE GEWICHTSZUNAHME TRAECHTIGER MUTTERTIERE
MEAN BODY WEIGHT INCREASE OF PREGNANT ANIMALS



N: MEHRFACHBELEGUNG - MULTIPLE POINTS
0:KONTR -CONTR 1: 0.1 MG/KG 2: 0.5 MG/KG 3: 2.5 MG/KG

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TR No.: 7219-94-077 . Tab. C.3.a.9

BOEHRINGER INGELHEIM KG REPRODUKTIONSTOXIKOLOGIE

SUBST./COMP. : SND 919CL2Y
VERS.NR./STUDY NO. : R03

TIERART/SPEC. : RATTEN / RATS
SEGM. 1

WURFDATEN / LITTER DATA
SUMMENWERTE / SUM VALUES
(GETOETET 14.-16. TAG / SACRIFICED DAY 14-16)

F_1-GENERATION

	KONTROLLE CONTROL	0.1 MG/KG	0.5 MG/KG	2.5 MG/KG
GESAMTZAHL DER TIERE TOTAL NUMBER OF ANIMALS	11	12	11	5
TODESFAELLE MATERNAL MORTALITY	0	0	0	0
TOTALRESORPTIONEN TOTAL RESORPTIONS	0	0	0	0
SPONTANWUERFE NATURAL DELIVERIES	0	0	0	0
TIERE MIT LEB. FETEN ANIM. WITH VIABLE FET.	10	11	11	4
GELBKOERPER CORPORA LUTEA	155	171	163	60
IMPLANTATIONEN IMPLANTATIONS	129	160	149	57
LEBENDE FETEN VIABLE FETUSES	122	146	139	54
RESORPTIONEN RESORPTIONS	7	14	10	3

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TR No.: 7219-94-077 Tab. C.3.a.10

BOEHRINGER INGELHEIM KG REPRODUKTIONSTOXIKOLOGIE

SUBST./COMP. : SND 919CL2Y
VERS.NR./STUDY NO. : R03

TIERART/SPEC. : RATTEN / RATS
SEGM. 1

WURFDATEN / LITTER DATA
MITTELWERTE / MEAN VALUES
(GETOETET 14.-16. TAG / SACRIFICED DAY 14-16)

F_1-GENERATION

		KONTROLLE CONTROL	0.1 MG/KG	0.5 MG/KG	2.5 MG/KG
CORPORA LUTEA / MUTTERT.	MW	15.5	15.5	14.8	15.8
CORPORA LUTEA / DAM	SD	2.0	1.9	1.3	1.4
IMPLANTATIONEN / MUTTERT.	MW	12.9	14.5	13.5	14.3
IMPLANTATIONS / DAM	SD	4.1	2.9	3.1	1.5
LEBENDE KEIME / MUTTERT.	MW	12.2	13.3	12.6	13.5
LIFE EMBRYOS / DAM	SD	4.2	3.1	3.4	1.3
RESORPTIONEN / MUTTERT.	MW	0.7	1.3	0.9	0.8
RESORPTIONS / DAM	SD	1.3	1.9	1.0	1.0
LEBENDE KEIME IN % IMPL.	MW	98.4	96.3	95.9	97.5
LIFE EMBRYOS IN % IMPL.	SD	4.4	5.9	4.2	3.5
RESORPTIONEN IN % IMPL.	MW	1.6	3.7	4.1	2.5
RESORPTIONS IN % IMPL.	SD	4.4	5.9	4.2	3.5
PRAEIMPLANTAT.-VERLUST	MW	10.9	1.5	3.8	3.8
PRE IMPLANTAT. LOSS %	SD	10.1	6.2	7.8	1.7

PROZENTWERTBERECHNUNG UEBER ARCSIN-TRANSFORMATIONEN
CALCULATIONS OF PERCENTAGES ARE ARCSINE-TRANSFORMATIONS

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C.3.b. Segment I in Rats: Fertility and Reproduction (Follow-up Study)

Document #(s): BI Document U92-0374
Upjohn TR 7219-94-078

Sponsor Volume: 1.43

Summary:

In the previous Segment I study in rats, daily treatment of females with 2.5 mg/kg PPX before and during gestation, and of males for 10 weeks before copulation significantly reduced the pregnancy rate. These studies did not determine the source of this impairment (i.e., male or female). Because of the well-established role of prolactin in the maintenance of rat pregnancy, and the ability of dopamine agonists to inhibit prolactin, it is reasonable to suspect that the female is the source of impairment. The present study was designed to provide evidence of this phenomenon by mating PPX-treated males with untreated females, and PPX-treated females with untreated males. A control group of untreated males and females, and a positive control group of treated males and females were also evaluated. PPX (2.5 mg/kg) was administered according to a schedule similar to that of the initial study. Males were sacrificed after copulation, and females were sacrificed on day 22 of gestation. In addition to the reproductive assessments, toxicokinetics and prolactin levels were also determined.

The main finding of the study was that the number and percentage of pregnant rats were significantly reduced in treated females regardless of whether the male partners had been treated. As in the preceding Segment I study, estrus was prolonged, and the total number of implantations in PPX-treated females was markedly reduced. Thus, the fertility impairment appears to result from an effect in the females rather than males. These findings were anticipated since pramipexole lowers serum prolactin as demonstrated in this study. The toxicokinetic analysis indicated that exposures in the pregnant rats at 2 hrs after dosing were higher than anticipated steady-state human levels (ng/ml). No adverse effects on litter parameters, and no teratogenic effects of PPX were evident. However, as in the preceding study, a low number of viable offspring from the treated groups limited the teratology information.

Methods:

Dosages: 2.5 mg/kg/day (Drug Lot: Batch VI; prepared in distilled water)

Route of Administration: oral (gavage)

Species/Number: 96 male and 96 nulliparous females

Allocated to four groups (24/sex):

Group 0:	control male; control female
1:	treated male; treated female
2:	treated male; untreated female
3:	treated female; untreated male

Mean initial weights/age:

males:	269g / 8 weeks
females:	203 g / 11 weeks

Parameters monitored/Intervals:

Clinical	-	daily
Body weight	-	weekly in males; daily in females
Food consumption	-	weekly

At Termination -

Males: Sacrificed after successful mating. Testes and epididymis were weighed, fixed in 7.5% formalin, and stored.

Females: Sacrificed on day 22 of gestation. Gross pathology, numbers of fetuses (viable and dead), corpora lutea, and resorptions. Ovaries were fixed in 7.5% formalin, and stored.

Fetuses: Live/dead; sex; one-half were examined for skeletal abnormalities, and one-half were examined for visceral and cephalic abnormalities.

Histopathology:

Fixed organs were embedded in paraplast. Sections were stained with hematoxylin-eosin.

Toxicokinetics:

Plasma levels were determined at sacrifice two hours after the last dose in 10/sex treated animals from the test groups (1-3), and in 5/sex control animals (group 0).

Prolactin determinations:

Serum prolactin levels were measured at sacrifice two hours after the last dose in 10 treated and 10 untreated animals per sex.

Statistics

Litter data were statistically evaluated using the Bartlett test, one-way ANOVA, Newman-Keuls test, Fisher's exact test, and the exact Wilcoxon test. Serum prolactin levels were evaluated using the Wilcoxon Rank Sum Test.

Results:

Effects in Males

Mortality: none

Clinical Signs:

Restlessness was observed from hrs after treatment.

Body Weight Gain:

Slight significant decrease in PPX-treated groups during week 2 (Fig. C.3.b.1).

Food Intake:

Significantly decreased in treated groups during week 1; significantly increased at later time points.

Necropsy:

No gross pathological changes were evident in any male rats. No significant differences in testicular weights among treatment groups were apparent.

Effects in Females

Mortality: none

Clinical Signs:

Restlessness was observed from hrs after treatment.

Body Weight Gain:

Body weight and body weight gain was significantly reduced in the PPX-treated groups during the first 2 weeks of treatment. No consistent effects on body weight in the treated animals occurred during gestation (Fig. C.3.b.2).

Food Intake:

Significantly increased in treated groups during week 2 prior to mating and during week 1 of gestation. During weeks 2 and 3, intake was significantly increased only in group 1.

TR No.: 7219-94-078

Fig. C.3.b.1.

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Dept.Exp.Path.and Tox.
Report/Study No.: R 39

Male - Bodyweight

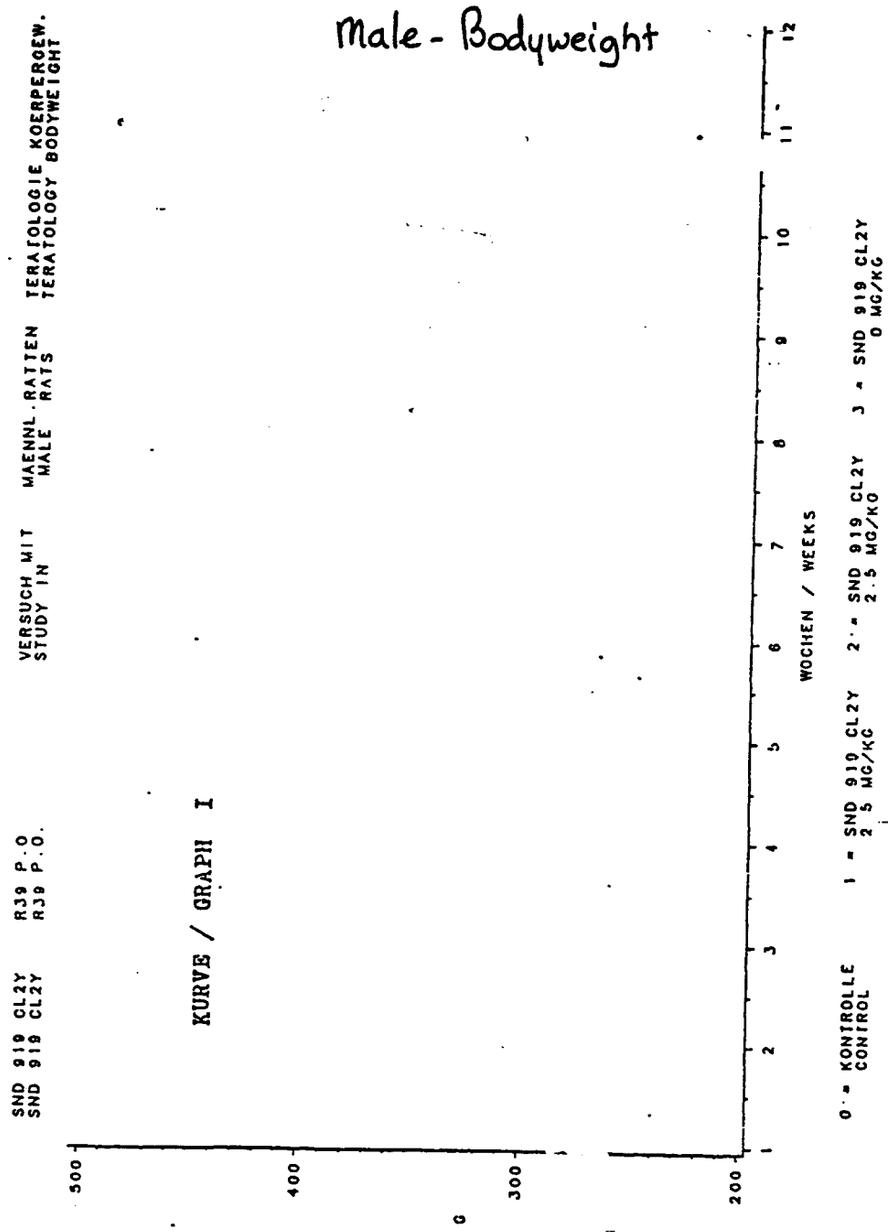
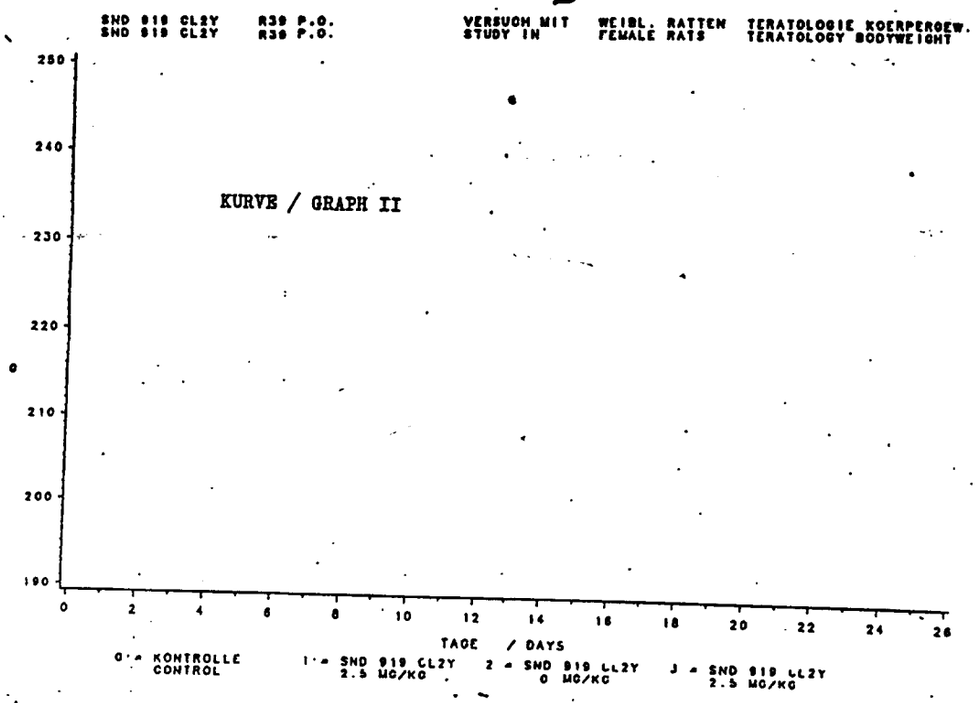
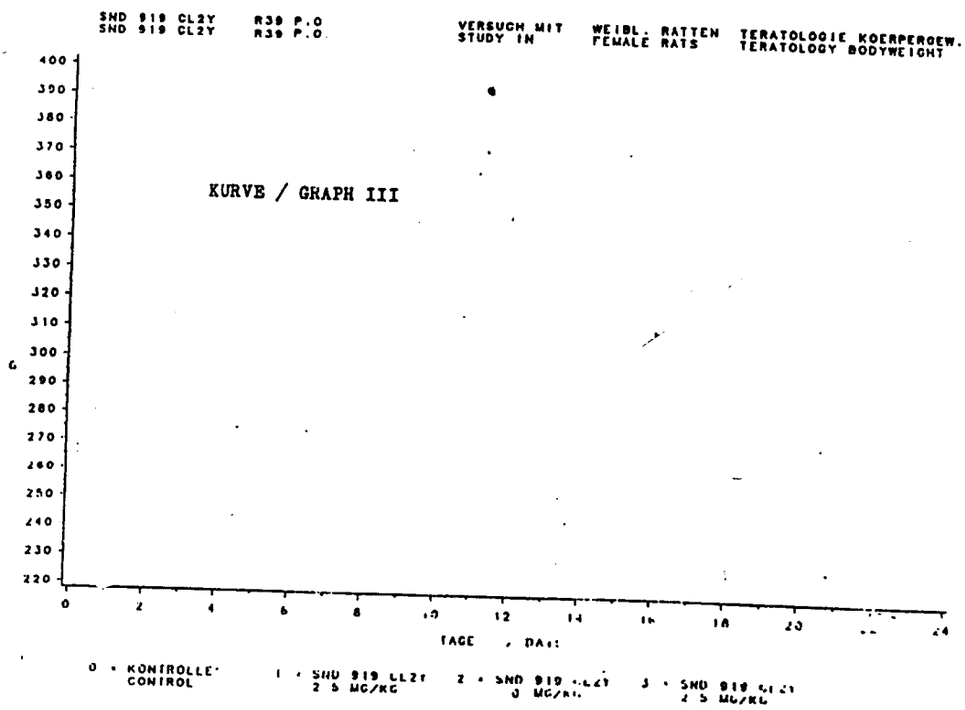


Fig. C.3.b.2.
Female - Bodyweight

Premating



Gestation



Estrous Cycle:

The estrus cycle was prolonged by 1 or 2 days in 13 of 24 females from each of the two drug-treated groups.

Conception:

Successful matings occurred in most groups within the first four days of mating. An additional cycle was required in 5 of 48 treated pairs. Two treated pairs did not successfully mate.

Fertility:

Successful pregnancies were recorded in 46 of 48 females of the untreated groups, and in 7 of 47 females of the treated groups.

Necropsy:

No gross pathological changes were found in any female rats, and there were no significant differences in ovary weights among treatment groups.

Effects on litter parameters

One group 3 female had a total resorption. The total number of implantations and pregnant dams in the PPX-treated groups was significantly reduced compared to controls (Tab. C.3.b.1). There were no significant differences among groups in the number of corpora lutea, fetuses (viable or dead), or resorptions per dam (Tab. C.3.b.2). Some differences in group means occurred when the dam with the total resorption was included in the calculation.

Effects on fetuses

The low pregnancy rate in PPX-treated animals provided a small number of fetuses for this assessment. No drug-related skeletal or visceral abnormalities were identified by the sponsor. The incidence of an additional rib in fetuses of PPX-treated dams (4/25 = 16% in Group 3 fetuses; 4/40 = 10% if PPX-treated fetuses are pooled; Tab. C.3.b.3) appears elevated relative to historical control data compiled by MARTA (Mid-Atlantic Reproduction and Teratology Association; Tab.C.3.b.4).

Histopathology

No drug-related lesions of the testes or epididymis were identified. Treated females (33/48) had an abnormally high number of corpora lutea and low number of follicles.

Tab. C.3.b.1

BOEHRINGER INGELHEIM KG

REPORT/STUDY NO. : R39

(SND 919 CL2Y , P.O. , RATTE / RAT , SEGMENT I)

WURFDATEN SUMMENWERTE / LITTER DATA SUM VALUES
KAISERSCHNITT / CAESAREAN SECTION

	KONTROLLE CONTROL	2.5 MG/KG	0 MG/KG	2.5 MG/KG a)	2.5 MG/KG b)
GESAMTZAHL DER TIERE TOTAL NUMBER OF ANIMALS	24	24	24	24	24
TODESFAELLE MATERNAL MORTALITY	0	0	0	0	0
TOTALRESORPTIONEN TOTAL RESORPTIONS	0	0	0	1	0
SPONTANWUERFE NATURAL DELIVERIES	0	0	0	0	0
TIERE MIT LEB. FETEN ANIM. WITH VIABLE FET.	23	2	23	4	5
GELBKOERPER CORPORA LUTEA	355	32	345	65	87
IMPLANTATIONEN IMPLANTATIONS	339	31	333	56	70
LEBENDE FETEN VIABLE FETUSES	330	31	308	53	53
MAENNLICH IN % MALE IN %	51	55	50	45	45
WEIBLICH IN % FEMALE IN %	49	45	50	55	55
TOTE FETEN DEAD FETUSES	0	0	0	0	0
RESORPTIONEN RESORPTIONS	9	0	25	3	17
FRUEH IN % EARLY IN %	89	0	68	100	100
SPAET IN % LATE IN %	11	0	32	0	0
MISSBILDUNGEN MALFORMATIONS	1	0	0	0	0
VARIATIONEN VARIATIONS	42	3	38	8	8

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a) = excluding, b) = including dam no.317 with total resorptions

Tab. C.3.b.2

BOEHRINGER INGELHEIM KG

REPORT/STUDY NO. : R39

(SND 919 CL2Y , P.O. , RATTE / RAT , SEGMENT I)

WURFDATEN MITTELWERTE / LITTER DATA MEAN VALUES
KAISERSCHNITT / CAESAREAN SECTION

		KONTROLLE CONTROL	2.5 MG/KG	0 MG/KG	2.5 MG/KG a)	2.5 MG/KG b)
GEWICHT / FET (G)	MW	5.20	4.93	5.24	5.07	5.07
WEIGHT / FETUS (G)	SD	0.22	0.44	0.24	0.34	0.34
PLAZ.GEW. / FET (G)	MW	0.42	0.40	0.41	0.43	0.43
PLAC. WEIGHT/ FETUS (G)	SD	0.04	0.02	0.05	0.07	0.07
CORPORA LUTEA / MUTTERT.	MW	15.4	16.0	15.0	16.3	17.4
CORPORA LUTEA / DAM	SD	1.5	2.8	2.4	1.0	2.7
IMPLANTATIONEN / MUTTERT.	MW	14.7	15.5	14.5	14.0	14.0
IMPLANTATIONS / DAM	SD	1.7	3.5	2.3	4.8	4.1
LEBENDE FETEN / MUTTERT.	MW	14.3	15.5	13.4	13.3	10.6
VIABLE FETUSES / DAM	SD	1.7	3.5	2.7	4.3	7.0
TOTE FETEN / MUTTERT.	MW	0.0	0.0	0.0	0.0	0.0
DEAD FETUSES / DAM	SD	0.0	0.0	0.0	0.0	0.0
RESORPTIONEN / MUTTERT.	MW	0.4	0.0	1.1	0.8	3.4
RESORPTIONS / DAM	SD	0.7	0.0	1.3	1.5	6.1
MISSBILDUNGEN / MUTTERT.	MW	0.1	0.0	0.0	0.0	0.0
MALFORMATIONS / DAM	SD	0.2	0.0	0.0	0.0	0.0
VARIATIONEN / MUTTERT.	MW	1.8	1.5	1.7	2.0	~~2.0~~ ok
VARIATIONS / DAM	SD	2.2	0.7	1.2	2.4	2.4
LEB. FETEN IN % IMPL.	MW	99.3	100.0	95.6	98.8	84.8
VIABLE FET. IN % IMPL.	SD	2.1	0.0	4.2	4.6	39.6
RESORPTIONEN IN % IMPL.	MW	0.7	0.0	4.4	1.2	15.2
RESORPTIONS IN % IMPL.	SD	2.1	0.0	4.2	4.6	39.6
PRAEIMPLANTAT.-VERLUST	MW	2.0	1.8	0.9	7.0	11.4
PRE IMPLANTAT. LOSS %	SD	2.7	3.6	2.9	14.2	13.4
POSTIMPLANTAT.-VERLUST	MW	0.7	0.0	4.4	1.2	15.2
POST IMPLANTAT. LOSS %	SD	2.1	0.0	4.2	4.6	39.6
MISSB. IN % LEB. FET.	MW	0.1	0.0	0.0	0.0	0.0
MALFORM. IN % VIAB. FET.	SD	0.8	0.0	0.0	0.0	0.0
VARIAT. IN % LEB. FET.	MW	17.2	18.1	22.0	14.5	14.5
VARIAT. IN % VIAB. FET.	SD	13.0	0.5	11.0	20.1	20.1

PROZENTWERTBERECHNUNG UEBER ARCSIN-TRANSFORMATIONEN
CALCULATIONS OF PERCENTAGES ARE ARCSINE-TRANSFORMATIONS

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a) = excluding, b) = including dam no.317 with total resorptions

TR No.: 7219-94-078

Tab. C.3.b.3

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Report/Study No.: R 39

SHD 919 CL 2 Y BEFUNDE AN FETEN RATTE
SHD 919 CL 2 Y EFFECTS ON FETUSES RATS

SUMMENWERTE / SUM VALUES

	KONTR. CONTR.	2.5 MG/KG	0 MG/KG	2.5 MG/KG
SKELETAL EXAMINATION				
NO. OF FETUSES EXAMINED	160	15	147	25
NO. OF FETUSES WITH MALFORMATIONS	1	0	0	0
NO. OF FETUSES WITH VARIATIONS	22	0	13	5
VISCERAL EXAMINATION				
NO. OF FETUSES EXAMINED	170	16	161	28
NO. OF FETUSES WITH MALFORMATIONS	0	0	0	0
NO. OF FETUSES WITH VARIATIONS	20	3	25	3
TYPE OF MALFORMATIONS				
CLEFT VERTEBRAE	1	0	0	0
TYPE OF VARIATIONS				
DUMB-BELL SHAPED VERTEBRAE	5	0	0	0
SHORT 13TH RIB (UNI- OR BILAT.)	16	0	13	1
ADDITIONAL 14TH RIB (PUNCTUAL)	0	0	0	4
GENERAL INCOMPLETENESS OF OSSIFICATION	1	0	0	0
DILATATION OF RENAL PELVIS (UNI- OR BILATERAL)	20	3	25	3
RUNTS	0	1	0	0
ADDITIONAL SKELETAL FINDINGS				
UNOSSIFIED STERNEBRA V	0	1	2	1
POORLY OSSIFIED STERNEBRA V	27	2	15	0
POORLY OSSIFIED STERNEBRAE IV+V	1	0	0	0

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Tab. C.3.b.4.

SKELETAL ANOMALIES ALL STUDIES

		FETAL INCIDENCE (%)			LITTER INCIDENCE (%)		
		AVG	S.D.	MAX	AVG	S.D.	MAX
STERNEBRAE							
1st fused to Manubrium		0.002	0.03	0.47	0.018	0.27	4.00
Multiple fusions		0.031	0.17	1.71	0.259	1.19	9.09
Agenesis		0.004	0.04	0.58	0.041	0.43	4.76
Split		0.126	0.51	5.88	0.540	2.19	21.74
Misaligned		0.471	1.44	10.19	2.990	7.37	47.37
Asymmetric		0.027	0.17	2.04	0.262	1.78	22.73
Duplicated		0.004	0.06	0.88	0.030	0.45	6.67
Misshapen		0.064	0.40	4.76	0.439	2.54	27.78
RIBS							
Agenesis		0.056	0.26	2.96	0.422	1.60	12.00
Branched/split		0.002	0.03	0.40	0.002	0.03	0.40
Cervical		0.394	0.75	5.00	2.814	4.80	25.00
Fused		0.034	0.13	0.68	0.287	1.11	5.88
Hypoplastic		0.926	2.81	21.64	2.778	8.53	61.90
Intercostal		0.004	0.06	0.84	0.025	0.37	5.56
Misshapen		0.270	0.96	7.50	1.628	5.42	42.11
* Supernumerary		3.199	5.30	25.14	14.776	22.97	77.78
Wavy		0.409	2.00	28.40	1.461	3.18	20.00
Bent		0.050	0.31	3.49	0.332	2.31	29.41
PELVIC GIRDLE							
Pelvic bone:	Agenesis	0.003	0.05	0.72	0.023	0.33	5.00
	Misaligned	0.002	0.02	0.26	0.037	0.39	4.17
Ilium:	Misshapen	0.003	0.05	0.72	0.025	0.37	5.56
Ischium:	Hypoplastic	0.013	0.10	1.20	0.110	0.87	10.00
SHOULDER GIRDLE							
Scapula:	Misshapen	0.008	0.07	0.82	0.076	0.66	6.67
APPENDICULAR SKELETON							
Forelimb							
Long bone:	Hypoplastic	0.006	0.09	1.41	0.041	0.61	9.09
	Misshapen	0.001	0.02	0.28	0.020	0.29	4.35
Metacarpal:	Agenesis	0.012	0.11	1.37	0.090	0.82	10.00
	Hypoplastic	0.021	0.14	1.36	0.136	0.95	10.00
Phalanx:	Misaligned	0.002	0.04	0.54	0.023	0.33	5.00
	Agenesis	0.003	0.04	0.59	0.019	0.28	4.17
	Clubbed	0.006	0.09	1.41	0.041	0.61	9.09
	Fused	0.004	0.05	0.82	0.030	0.45	6.67
Hindlimb							
Long bone:	Small	0.006	0.09	1.41	0.041	0.61	9.09
	Hypoplastic	0.002	0.03	0.47	0.002	0.03	0.47
	Misshapen	0.005	0.04	0.47	0.041	0.41	4.35
Metacarpal:	Agenesis	0.004	0.06	0.88	0.030	0.45	6.67
Phalanx:	Agenesis	0.024	0.22	2.37	0.158	1.43	16.00
	Clubbed	0.006	0.09	1.41	0.041	0.61	9.09
	Supernumerary	0.005	0.07	1.03	0.018	0.27	4.00
	Misaligned	0.044	0.65	9.73	0.169	2.51	37.50
Talus:	Advanced	0.013	0.16	2.35	0.039	0.41	4.55

Serum Prolactin levels

A marked lowering of serum prolactin was recorded in most PPX-treated rats (Tab. C.3.b.5).

Influence of SND 919 Cl2 on Serum Prolactin Levels in Rats

Groups	Dose	Sex	Animal-No.	Prolactin (ng/ml)
0/3	Control	m	054	120.87
			059	133.72
			065	99.95
			068	28.11
			069	34.57
			351	31.30
			355	77.08
			357	357.44
			358	53.22
			362	103.99
			Median	88.52
			NI	10
1/2	2.5 mg/kg SND 919 CL2	m	154	< 0.39
			156	< 0.39
			263	0.71
			265	0.72
			268	< 0.39
			269	< 0.39
			270	1.43
			271	3.01
			272	10.37
			274	2.19
			Median	0.71 ***
			NI	10
0/2	Control	f	009	252.09
			015	186.42
			019	15.35
			021	409.13
			205	272.42
			207	294.12
			209	287.99
			215	238.15
			218	91.73
			223	195.20
			Median	245.12
			NI	10
1/3	2.5 mg/kg SND 919 CL2	f	112	< 0.39
			113	< 0.39
			114	< 0.39
			115	< 0.39
			118	236.64
			119	< 0.39
			312	< 0.39
			316	< 0.39
			317	72.26
			318	< 0.39
			Median	< 0.39 ***
			NI	10

*** = p < 0.001

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Toxicokinetics

Plasma concentrations of PPX were determined 2 hrs after dosing. Levels were higher in females than in males (Tab. C.3.b.6).

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group no.	mean ± SD	
	females	males
1	158.3 ± 47.18	74.7 ± 23.74
2	-	85.0 ± 34.83
3	164.1 ± 40.95	-

The plasma concentrations of SND 919 CL 2 Y in female animals were clearly higher than in males.

For both sexes, there was no relevant difference between the results from different groups (females: group no. 1 vs. no 3, males: group no. 1 vs. no. 2).

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