Annex I to the CLH report

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation),
Annex VI, Part 2

International Chemical Identification:

3,4-dimethyl-1*H*-pyrazol-1-ium dihydrogen phosphate

EC Number: 424-640-9

CAS Number: 202842-98-6

Index Number: /

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CONTENTS

1 PHYSICAL HAZARDS

Not evaluated in this CLH dossier.

2 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Not evaluated in this CLH dossier

3 HEALTH HAZARDS

3.1 Acute toxicity - oral route

3.1.1 Animal data

3.1.1.1 Acute oral toxicity study in rats (Anonymous, 1997)

Study reference

Anonymous, 1997

Detailed study summary and results

Test type

GLP

Test substance

- 3,4-dimethyl-1*H*-pyrazol-1-ium dihydrogen phosphate
- *Degree of purity:* 97.1 %

Test animals

- *Species/strain/sex:* Rat / Wistar / male and female
- *Nb. of animals per sex per dose:* 3 animals/Exp
- *Age and weight at the study initiation:* young adults ; 150 – 300 g

Administration/exposure

- *Mode of administration:* oral, gavage
- *Duration of test/exposure period:* single exposure
- *Doses/concentration levels, rationale for dose level selection:* first Exp: 2000 mg/kg bw (in males)
  Second Exp: 200 mg/kg bw (in males)
  Third Exp: 200 mg/kg bw (in females)
- *Post exposure observation period:* 14 days
- *Control group and treatment:* /
- *Vehicle:* 0,5 % Tylose CB 30000 in aqua bidest

Results and reliability

- *LD_{50} or LC_{50} value with confidence limits if calculated:* between 200 and 2000 mg/kg bw

- *Nb. of deaths at each dose level:*

Table 1: Mortality and time of death

Dose level (in mg/kg bw)	2000	200	
	M	M	F
Nb animals examined	3	3	3
Nb of animals which died	2	0	0
After 3 h	1	/	/
After 1 D	2	/	/

Additional information that may be needed to adequately assess data for reliability:

- *Clinical signs:* 2000 mg/kg bw: all males exhibited dyspnoea, apathy, abdominal position, staggering, atonia. 2 males showed narcotic like state and poor general state, while 1 male had impaired general state, piloerection and sunken flanks.

  200 mg/kg bw: in males: no clinical signs observed.

  In females: all animals exhibited impaired general state, dyspnoea, staggering and piloerection.
- *Necropsy findings, including doses affected, severity and number of animals affected:*
  - *Animals that died:* the 2 males which died showed moderate dilatation of the urinary bladder, 1 male had erosion/ulcere in glandular stomach and slight hyperemia.
  - *Sacrificed animals:* no findings observed.

3.1.2 Human data

No human data available

3.1.3 Other data

No other data available

3.2 Acute toxicity - dermal route

3.2.1 Animal data

3.2.1.1 Acute dermal toxicity study in rats (Anonymous, 2017)

Study reference

Anonymous, 2017

Detailed study summary and results

Test type

OECD TG 402

GLP

Test substance

- 3,4-dimethyl-1*H*-pyrazol-1-ium dihydrogen phosphate
- *Degree of purity:* 99.4 %

Test animals

- *Species/strain/sex:* Rat / Wistar / both sexes
- *Nb. of animals per sex per dose:* 5/sex/dose
- *Age and weight at the study initiation:* approx. 8 weeks for males and 12 weeks for females

Administration/exposure

- *Mode of administration:* single application to the clipped skin (dorsal and dorsolateral parts of the trunk)
- *Duration of test/exposure period:* single exposure of 24 h
- *Doses/concentration levels, rationale for dose level selection:* 2000 or 5000 mg/kg bw
- *Post exposure observation period:* 14 d
- *Control group and treatment:* /
- *Vehicle:* deionized water
- *Area covered (e.g. x% of body surface):* at least 10 % of the total body surface (about 40 cm^2)
- *Occlusion:* semi-occlusive dressing
- *Total volume applied:* 10 ml/kg bw
- *Removal of test substance:* afterwards removal of the dressing, rinsing of the application site with warm water.

Results and reliability

- *LD_{50} or LC_{50} value with confidence limits if calculated:* > 5000 mg/kg bw
- *Nb. of deaths at each dose level:* no mortality occurred during the study period

Additional information that may be needed to adequately assess data for reliability

- *Time of death (provide individual animal time if less than 24 hours after dosing):* /
- *Clinical signs:* no clinical signs (local or systemic) observed
- *Necropsy findings, including doses affected, severity and number of animals affected:* no abnormalities observed.

3.2.2 Human data

No human data available

3.2.3 Other data

No other data available

3.3 Acute toxicity - inhalation route

3.3.1 Animal data

3.3.1.1 Acute inhalation toxicity study in rats (Anonymous, 1997)

Study reference

Anonymous, 1997

Detailed study summary and results

Test type

GLP

Similar to OECD TG 403

Test substance

- 3,4-dimethyl-1*H*-pyrazol-1-ium dihydrogen phosphate
- *Degree of purity:* 97.1 %
- *Particle size of dust and mist given as mean mass aerodynamic diameter (MMAD) and geometric standard deviation or give other specifications:* MMAD of 12.2 µm

  Dust
- *Type or preparation of particles (for studies with aerosols):* /

Test animals

- *Species/strain/sex:* Rat / Wistar / both sexes
- *Nb. of animals per sex per dose:* 5/sex/group
- *Age and weight at the study initiation:* approx. 8-9 w

Administration/exposure

- *Type of inhalation exposure and test conditions:* head-nose inhalation system
- *Duration of test/exposure period:* single exposure of 4 h
- *Doses/concentration levels, (ppmV (parts per million per volume) for gases, mg/l for vapours, mg/L for dusts and mists) and rationale for dose level selection:* 5.5 mg/L
- *Post exposure observation period:* 14 d
- *Control group and treatment:* /

Results and reliability

- *LD_{50} or LC_{50} value with confidence limits if calculated:* > 5.5 mg/L
- *Nb. of deaths at each dose level:* no mortality observed during the study period

Additional information that may be needed to adequately assess data for reliability

- *Time of death (provide individual animal time if less than 24 hours after dosing):* /
- *Clinical signs:* All animals exhibited irregular respiration, accelerated respiration, crust formation in nose, piloerection. After day 3, all animals recovered.
- *Necropsy findings:* no effects observed.

3.3.2 Human data

No human data available

3.3.3 Other data

No other data available

3.4 Skin corrosion/irritation

Hazard class not assessed in this dossier

3.5 Serious eye damage/eye irritation

Hazard class not assessed in this dossier

3.6 Respiratory sensitisation

No available study

Hazard class not assessed in this dossier

3.7 Skin sensitisation

No available study

Hazard class not assessed in this dossier

3.8 Germ cell mutagenicity

Hazard class not assessed in this dossier

3.9 Carcinogenicity

Hazard class not assessed in this dossier

3.10 Reproductive toxicity

3.10.1 Animal data

3.10.1.1 Two-generation reproduction toxicity study (Anonymous, 2004)

Study reference

Anonymous, 2004

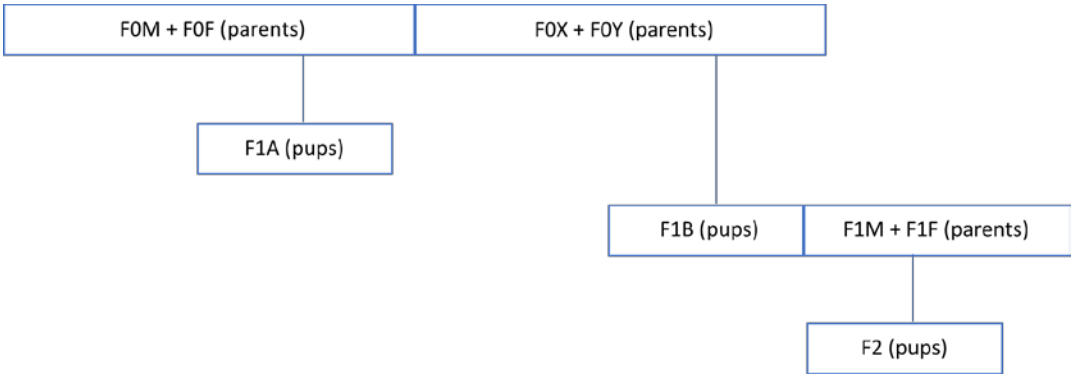
Detailed study summary and results

Test type

OECD TG 416

GLP

Figure 1: Test group and experimental procedure



Test substance

- DMPP
- *Degree of purity:* 97 %

Test animals

- *Species/strain/sex:* Rat / Wistar / both sexes
- *Nb. of animals per sex per dose:* 25/sex/dose for F0 and F1 parental generation
- *Age and weight at the study initiation:* 35 ± 1 days old and approx. 111.4 g in males and 99.1 g in females.

Administration/exposure

- *Route of administration:* oral, diet
- *Duration and frequency of test/exposure period:*
    - The parental generation, named F0M for males and F0F for females, received the test substance at a concentration of 0, 20, 100 and 500 mg/kg bw/d during a premating period of min 75 days. After this period, F0M and F0F from the same dose group were mated at a ratio of 1:1. F0F continued to be exposed to the test substance during gestation and lactation period of 21 day.

- The F1A generation pups were observed and examined until post-natal day 4 (day of standardization group) or post-natal day 21. Based on the high maternal toxicity as well as the high developmental toxicity at the highest dose group (500 mg/kg bw/d), all surviving F1A pups were killed on day 21 post-partum and examined without selecting any F1A pups for a second parental generation.
- After that, a second F0 parental generation begun with the same animals used for the first parental generation. This generation was named F0X for males and F0Y for females, and were given test substance at a concentration of 0, 20, 100 and 300 mg/kg bw/d. Animals received the test substance during a premating period of 10 weeks. Animals were remated, if possible with the same partner as for the first mating (as so-called F0M and F0F rats), to produce a second litter (F1B generation pups). After weaning of F1B pups, the F0 generation parental animals (F0X and F0Y) were sacrificed.
- After weaning of the F1B pups, 25 males and 25 females by group were selected to be the F1 parental generation (designated as F1M for males and F1F for females). Animals were exposed to the test substance at a concentration of 0, 20, 100 or 300 mg/kg bw/d during a premating period of minimum 75 days. After this premating period, F1M and F1F were mated at a ratio of 1:1. The F1F were allowed to litter and rear their pups (F2 pups generation) until day 4 (standardization) or 21 after parturition. Shortly after weaning, the F1 parental generation were sacrificed.

- *Doses/concentration levels, rationale for dose level selection:* 0, 20, 100 and 500/300 mg/kg bw/d
- *Vehicle:* /

Description of test design

- *Details on mating procedure (M/F ratios per cage, length of cohabitation, proof of pregnancy):* ratio 1:1
- *Premating exposure period for males and females:* at least 75 days
- *Standardization of litters (yes/no and if yes, how and when):* yes, on day 4 post-partum (to contain 4 males and 4 females)
- *Estrous cycle length and pattern, sperm examination, clinical observations performed and frequency:*
  - *Estrous cycle:* evaluated for a min. of 3 weeks prior to mating and continued throughout the mating period.
  - *Sperm parameters:* analysed immediately after necropsy.

Results and discussion

For P adults (per dose): F0M and F0F parents:

- *Actual dose received by dose level by sex if known:*

Table 2: Mean actual test substance intake (in mg/kg bw/d)

	Low dose	Mid dose	High dose
Males			
W 0 to 18	20.4	102.4	505.3
Females			
Premating period (W 0 to 10)	20.7	103.7	530.7
Gestation period (D 0 to 20)	20.6	100.6	491.3
Lactation period (D 1 to 14)	19.1	95.2	388.0

- *Nb. of animals at the start of the test and mating:* 25/sex/group
- *Time of death during the study and whether animals survived to termination:* one male of the mid dose group was found dead on the study week 16 (at necropsy, malignant oligodendroglioma in brain was observed) and one female of this group was sacrificed in a moribund state on GD 22 (poor general state, blood in bedding, vaginal haemorrhage, signs of anaemia and piloerection from GD 19 until sacrifice. At necropsy, malignant lymphoma with several concurrent gross abnormalities and histopathological findings were noted)
- *Clinical observations:*
    - During premating period: no treatment-related effects observed.
    - No sperm in vaginal smear in 3 F of the highest dose.
    - No pups delivered in 1 F, 0 F, 1 F and 5 F, resp. at 0, 20, 100 and 500 mg/kg bw/d.
- *Food consumption:*

Table 3: Mean food consumption (in g/animal/day)

Dose level (in mg/kg bw/d)	0	20	100	500
In males				
W 0 to 18	21.7	21.5	21.9	20.1 (± -7 % compared to control)
In females				
Premating period (W 0 to 10)	16.2	15.8	16.0	15.1 (± -7 % compared to control)
Gestation period (D 0 to 20)	19.9	19.7	19.5	17.3 (± -13 % compared to control)
Lactation period (D 1 to 14)	36.5	37.4	37.6	26.9 (± -26 % compared to control)

- *Body weight data:*

Table 4: Mean body weight data in males (in g)

Dose level (in mg/kg bw/d)	0	20	100	500
W 0	111.2	112.2	111.6	110.4
W 5	284.3	286.0	287.5	279.1
W 10	362.6	362.7	358.6	338.4*
W 15	401.2	401.7	399.6	364.8**
W 18	418.9	415.2	409.2	365.4**
BWG W 0 to 18	307.7	303.0	297.4	255.0**

Table 5: Mean body weight data in females (in g)

Dose level (in mg/kg bw/d)		0	20	100	500	HCD range
Premating period	W 0	99.2	99.1	98.4	99.5	
	W 5	179.6	173.2	174.4	175.1	
	W 10	210.9	205.1	205.8	199.8*	
	BWG W 0 to 10	111.8	105.9	107.3	100.3**	
Gestation period	D 0	216.2	209.7	210.4	204.9	152.3 – 288.3
	D 7	237.1	230.7	229.8	219.9**	174.6 – 320.4
	D 14	258.2	251.4	250.9	232.8**	189.7 – 356.6
	D 20	305.9	302.4	297.9	276.6**	220.4 – 413.3
	BWG D 0 to 20	89.6	92.7	87.5	71.7**	
Lactation period	D 1	231.6	235.9	232.1	216.4*	179.2 – 330.4
	D 4	242.4	245.1	243.5	221.9**	184.8 – 328.5
	D 7	250.5	250.6	247.5	229.7**	194.3 – 350.3
	D 14	262.9	261.6	262.6	239.3**	204.2 – 353.0
	D 21	256.6	253.0	254.7	235.7**	199.8 – 337.9
	BWG D 0 to 21	25.0	17.1	22.6	19.4	

- *Haematological and clinical biochemistry findings:*

Table 6: Haematological and biochemical data

	Males				Females			
Dose level (in mg/kg bw/d)	0	20	100	500	0	20	100	500
WBC (giga/L)	5.94	NT	NT	6.58	3.18	NT	NT	3.47
RBC (tera/L)	9.21	NT	NT	9.35	8.63	NT	NT	8.74
Hb (mmol/L)	9.9	NT	NT	10.1	9.9	NT	NT	10.3*
Ht (L/L)	0.456	NT	NT	0.464	0.456	NT	NT	0.461
MCV (fl)	49.6	NT	NT	49.6	52.9	NT	NT	52.7
MCH (fmol)	1.07	NT	NT	1.08	1.15	NT	NT	1.17
MCHC (mmol/L)	21.60	NT	NT	21.75	21.78	NT	NT	22.25
Plt (giga/L)	811	NT	NT	840	823	NT	NT	836
HQT (sec)	35.0	NT	NT	33.4	31.4	NT	NT	32.3
ALT (µkat/L)	0.64	NT	NT	0.77	0.61	NT	NT	0.59
AST (µkat/L)	2.35	NT	NT	2.41	2.02	NT	NT	2.38*
ALP (µkat/L)	3.35	NT	NT	3.32	2.41	NT	NT	2.60
SGGT (nkat/L)	5	NT	NT	8	6	NT	NT	6
GLDH (nkat/L)	134	NT	NT	169	82	NT	NT	209**
Tot. prot. (g/L)	69.2	NT	NT	69.44	68.91	NT	NT	72.29
Chol (mmol/L)	1.95	NT	NT	2.95**	1.42	NT	NT	1.90*

- *Hormones:*

Table 7: Hormone data

	Males				Females			
Dose level (in mg/kg bw/d)	0	20	100	500	0	20	100	500
ALD (pmol/L)	388.03	NT	NT	248.94	1043.58	NT	NT	622.91**

CC (nmol/L)	444.38	NT	NT	307.67	1728.50	NT	NT	1010.29**
T (nmol/L)	15.85	NT	NT	5.10	1.82	NT	NT	0.90**
LH (µg/L)	1.06	NT	NT	1.08	23.57	NT	NT	2.49**
FSH (µg/L)	10.83	NT	NT	8.19	7.53	NT	NT	5.35**
E_2 (pmol/L)	-	-	-	-	163.86	NT	NT	113.68

- *Effects on sperm:* not examined
- *Nb. of females cycling normally and cycle length:* mean days from estrous to estrous: 4.0, 3.8, 3.9 and 4.8** days, resp. at 0, 20, 100 and 300 mg/kg bw/d (HCD (oct 2000 – Jan 2002): 3.8 – 5.4 days)
- *Cohabitation data:*
  - *Males placed with females:* 25 in all groups
  - *Males mated (male mating index):* 25 (100 %), 25 (100 %), 25 (100 %) and 22 (88 %), resp. at 0, 20, 100 and 300 mg/kg bw/d

    3 males did not mated at the highest dose

    HCD range for male mating index: 92 to 100 %
  - *Males without females pregnant:* 1, 0, 1 and 8* males, resp. at 0, 20, 100 and 500 mg/kg bw/d
  - *Male fertility index:* 96, 100, 96 and 68 %, resp. at 0, 20, 100 and 500 mg/kg bw/d (HCD (oct 2000 – Jun 2002): 84 – 100 %)

    (When F0M and F0F were remated (renamed F0X and F0Y and exposed to 0, 20, 100 and 300 mg/kg bw/d), only 1 male of the mid dose and 1 male of the highest dose remained infertile).
- *Female reproduction data:*

Table 8: Female reproduction data

Dose level (in mg/kg bw/d)		0	20	100	500	HCD (10/00 – 06/02)
Nb of females		25	25	25	25	
Nb of females mated (mating index in %)		25 (100 %)	25 (100 %)	25 (100 %)	22 (88 %)	
Mating day until DPC 0	Mean	2.8	2.7	2.3	3.5	2.1 – 3.6
	D 1 to 4	25	25	25	16	
	D 5 to 8	0	0	0	6	
	D 9 to 14	0	0	0	0	
	D 15 to 21	0	0	0	0	
Nb of females pregnant		24	25	24	17	
Female fertility index (in %)		96	100	96	77	84 – 100 %

When F0M and F0F were remated (renamed F0X and F0Y and exposed to 0, 20, 100 and 300 mg/kg bw/d), only 1 female of the mid dose and 1 female of the highest dose remained infertile.

- *Mean duration of gestation (calculated from day 0 of pregnancy):* 21.9, 21.8, 21.8 and 22.6** days, resp. at 0, 20, 100 and 500 mg/kg bw/d (HCD (oct 2000 – Jun 2002): 21.7 – 22.2 days)

- *Nb. of implantations, corpora lutea, litter size:* /
- *Nb. of pre- and post-implantation loss:* /
- *Nb. of dams with abortions, early deliveries, stillbirths, resorptions and/or dead fetuses:*
    - *Nb. of females with liveborn pups (gestation index):* 24 (100 %), 25 (100 %), 23 (96 %) and 17 (100 %) females, resp. at 0, 20, 100 and 500 mg/kg bw/day.
    - *Nb. of females with stillborn pups:* 5, 2, 2 and 13** females, resp. at 0, 20, 100 and 500 mg/kg bw/d (No females with all stillborn pups).
- *Nb. of live births:*

Table 9: Delivery data

Dose level (in mg/kg bw/d)	0	20	100	500	HCD (10/00 – 06/02)
Mean nb of F1A pups delivered	11.0	10.7	11.0	8.5**	9.8 – 11.7
Tot nb of pups	264	268	254	145	
Nb of liveborn pups	252	266	252	117**	
Live birth index (in %)	95	99	99	81	96 – 100
Nb of stillborn pups (in %)	12 (4.5)	2 (0.7)	2 (0.8)	28** (19.0)	

- *Necropsy findings:* /
- *Organ weight:* /
- *Histopathological findings:* /
- *Body weight change and gravid uterine weight, including optionally, body weight change corrected for gravid uterine weight:* /

For F1 pups/litters (per dose): F1A pups

- *Litter data:*

Table 10: Litter data

Dose level (in mg/kg bw/d)	0	20	100	500	HCD (oct 2000 – Jun 2002)
Mean nb of pups delivered	11.0	10.7	11.0	8.5**	9.8 – 11.7
Tot nb of pups	264	268	254	145	
Nb of liveborn pups	252	266	252	117**	
Nb of stillborn pups	12	2	2	28**	
Nb of pups died	2	0	1	13**	
Nb of pups cannibalized	11	0	1	18**	

Total litter losses: in 1 dam in control group and in 3 dams of the highest dose:

1 control dam cannibalized 7 (out of 13) pups on dpp 2 (all other pups of this dams were stillborn).

2 dams of the highest dose cannibalized all of their liveborn pups on dpp 2.

1 other dam of the highest dose had 4 (out of 8 pups) which were stillborn and the remaining pups died or were cannibalized by their mother.

- *Mean nb. of live pups per litter:*

Table 11: Mean nb of live pups per litter

Dose level (in mg/kg bw/d)	0	20	100	500
PND 1	10.1	10.6	10.9	5.2
PND 4 (preculling)	10.0	10.6	10.9	5.1
PND 4 (postculling)	7.5	8.0	7.7	4.9
PND 7	7.5	8.0	7.7	4.9
PND 14	7.5	8.0	7.7	4.9
PND 21	7.5	8.0	7.7	4.9

- *Sex ratio:*
  - *At day 0:* 51.6/48.4, 45.1/54.9, 47.6/52.4 and 49.6/50.4 % of males/females, resp. at 0, 20, 100 and 500 mg/kg bw/d.
  - *At day 21:* 52.8/47.2, 48.2/51.8, 49.7/50.3 and 47.0/53.0 % of males/females, resp. at 0, 20, 100 and 500 mg/kg bw/d.
- *Mortality:*

Table 12: Pups mortality

Dose level (in mg/kg bw/d)	0	20	100	500
At D 0	1 (0.4)	0	0	2 (1.7)
Between D 1 to 4 (in %)	12 (4.8)	0	0	29 (25)
Between D 5 to 7	0	0	0	0
Between D 8 to 14	0	0	0	0
Between D 15 to 21	0	0	0	0

- *Viability index (pups surviving 4 days/total births):* 95, 100, 99 and 74 %, resp. at 0, 20, 100 and 500 mg/kg bw/d (nb of surviving pups: 239, 266, 250 and 86**, resp. at 0, 20, 100 and 500 mg/kg bw/d) (HCD: 96 to 100 %)
- *Survival index at weaning:* 100 % in all groups
- *Mean litter or pup weight by sex and with sexes combined:*

Table 13: Mean pup body weight (in g)

Dose level (in mg/kg bw/d)		0	20	100	500
PND 1	M	6.1	6.4	6.4	5.7
	F	5.7	6.0	6.0	5.2*
	M+F	5.9	6.2	6.2	5.3**
PND 4 (preculling)	M	9.3	9.6	9.5	8.5
	F	9.0	9.2	9.0	8.1
	M+F	9.2	9.4	9.2	8.2*
PND 4 (postculling)	M	9.3	9.7	9.5	8.5
	F	9.0	9.2	9.1	8.1*
	M+F	9.2	9.5	9.3	8.2*
PND 7	M	14.9	15.1	14.8	12.1**
	F	14.4	14.5	14.3	11.6**
	M+F	14.7	14.8	14.6	11.8**

PND 14	M	29.5	29.5	29.1	24.2**
	F	29.0	28.7	28.5	23.5**
	M+F	29.3	29.1	28.8	23.8**
PND 21	M	47.5	47.5	47.0	39.4**
	F	46.0	46.1	45.8	38.5**
	M+F	46.8	46.8	46.4	38.9**

- *Body weight change:*

Table 14: Mean pup body weight change (in g)

Dose level (in mg/kg bw/d)		0	20	100	500
PND 1 to 4	M	3.2	3.2	3.1	2.8
	F	3.2	3.1	3.1	2.7
	M+F	3.2	3.2	3.1	2.8
PND 4 to 21	M	38.2	37.8	37.5	30.9**
	F	37.1	37.0	36.8	30.4**
	M+F	37.7	37.4	37.2	30.6**

- *Necropsy observation:*
  - *Total nb. of pups with necropsy findings:* 16, 4, 4 and 16 pups, resp. at 0, 20, 100 and 500 mg/kg bw/d
  - *Litter incidence:* 12, 3, 3 and 7, resp. at 0, 20, 100 and 500 mg/kg bw/d
  - *Mean % of affected pups/litter:* 7.1, 1.4, 1.5 and 16.2 %, resp. at 0, 20, 100 and 500 mg/kg bw/d
- *Pups organ weight:*

Table 15: Pups organ weight data (in g or %)

Dose level (in mg/kg bw/d)		0	20	100	500	HCD range (Oct 00 – Jun 02)
Brain	Abs	1.465	1.479	1.474	1.422*	0.888 – 1.697
	Rela	3.148	3.162	3.211	3.699**	1.773 – 5.821
Thymus	Abs	0.216	0.219	0.216	0.177*	0.042 – 0.322
	Rela	0.462	0.467	0.470	0.459	0.198 – 0.662
Spleen	Abs	0.222	0.223	0.212	0.159**	0.027 – 0.392
	Rela	0.472	0.472	0.460	0.404**	0.136 – 0.741

- *External, soft tissue and skeletal malformations and other relevant alterations:* /
- *Nb. and percent of fetuses and litters with malformations (including runts) and/or variations as well as description and incidences of malformations and main variations (and/or retardations):* /
- *Data on physical landmarks in pups and other postnatal developmental data:* /
- *Data on functional observations:* /

For P adults (per dose): F0X and F0Y parents

- *Actual dose received by dose level by sex if known:*

Table 16: Mean actual test substance intake (in mg/kg bw/d)

		Low dose	Mid dose	High dose
Males				
W 0 to 18		19.8	99.2	297.4
Females				
Premating period	W 0 to 10	20.2	100.2	301.1
Gestation period	D 0 to 20	22.1	112.6	320.9
Lactation period	D 1 to 14	21.3	103.9	276.8

- *Nb. of animals at the start of the test:* 25, 25, 24 and 25 males and 25, 25, 24 and 25 females, resp. at 0, 20, 100 and 300 mg/kg bw/d.
- *Time of death during the study and whether animals survived to termination:* one female of the control group was sacrificed on GD 23 (unable to deliver completely and poor general state (chromodacryorrhea, hypothermia and piloerection). Furthermore, one female of the highest dose was found dead during the study week 17 (necropsy revealed severe chronic progressive nephropathy).
- *Clinical signs:* no treatment related effects observed
- *Mean food consumption:*
    - *Males:* W 0 to 17: 21.8, 21.5, 21.6 and 20.4 g/animal/day, resp. at 0, 20, 100 and 300 mg/kg bw/d
    - *Females:* premating period (W 0 to 10): 16.5, 16.3, 16.3 and 15.4 g/animal/day, resp. at 0, 20, 100 and 300 mg/kg bw/d

      Gestation period (D 0 to 20): 20.6, 20.7, 20.6 and 18.6 g/animal/day, resp. at 0, 20, 100 and 300 mg/kg bw/d

      Lactation period (D 1 to 14): 39.2, 39.9, 38.1 and 31.6 g/animal/day, resp. at 0, 20, 100 and 300 mg/kg bw/d
- *Body weight data:*

Table 17: Body weight data (in g)

Dose level (in mg/kg bw/d)		0	20	100	300
Males					
W 0		418.1	418.8	411.0	359.6**
W 5		440.0	436.1	431.2	392.4**
W 10		452.8	453.3	445.9	408.4**
W 15		462.6	462.5	457.7	418.7**
W 17		471.0	468.3	464.0	425.6**
BWG (W 0 to 17)		52.9	49.5	53.0	66.0*
Females					
Premating period	W 0	238.1	237.4	236.7	217.0**
	W 5	243.2	239.5	236.4	226.9**
	W 10	248.2	245.4	245.9	233.1*
	BWG (W 1 to 10)	10.2	7.9	9.2	16.1*

Gestation period	D 0	248.6	246.8	245.0	231.6**
	D 7	269.5	268.1	255.3	249.3**
	D 14	288.2	288.2	283.1	262.2**
	D 20	338.6	341.4	331.2	304.6**
	BWG (D 0 to 20)	90.1	94.6	86.2	73.0**
Lactation period	D 1	264.2	266.5	266.9	244.8**
	D 4	273.8	278.4	273.3	252.3**
	D 7	279.4	281.9	280.8	258.1**
	D 14	286.5	293.3	287.9	264.8**
	D 21	276.5	280.1	281.6	265.9
	BWG (D 1 to 21)	12.4	13.6	14.7	21.1

- *Haematological and clinical biochemistry findings:*

Table 18: Biological data

	Males				Females			
Dose level (in mg/kg bw/d)	0	20	100	300	0	20	100	300
ALT (µkat/L)	0.68	0.80	0.73	0.76	0.66	0.66	0.58	0.70
AST (µkat/L)	2.00	3.02	2.45	2.63	2.60	2.45	2.13	3.18
ALP (µkat/L)	1.09	1.13	1.20	1.07	0.85	0.87	0.72	0.93
SGGT (nkat/L)	1	2	3	2	0	0	1	0
GLDH (nkat/L)	201	312	251	131*	354	331	141*	104**
Tot. prot. (g/L)	72.68	73.95	73.62	73.44	73.56	74.27	74.17	74.04
Chol (mmol/L)	2.31	2.31	2.60**	2.84**	2.49	2.46	2.44	2.48

- *Effects on sperm:*

Table 19: Sperm evaluation

Dose level (in mg/kg bw/d)	0	20	100	300	HCD range
Mean tot spermatids/g testis	120	NT	NT	117	94 - 144
Mean tot sperm/g cauda epididyma	585	NT	NT	562	517 – 727
Mean % normal sperm	98.1	NT	NT	97.6	94.8 – 99.1
Mean % abnormal sperm	1.9	NT	NT	2.4	0.9 – 5.2
Mean % motility	92	90	91	89	81 - 92

HCD: from 03/00 to 03/02 (16 studies during this period – Wistar rat)

- *Cohabitation data:*

Table 20: Male cohabitation data

Dose level (in mg/kg bw/d)	0	20	100	300
Males placed with females	25	25	24	25
Males mated	25	25	24	25
Males with females pregnant	23	23	23	23
Male fertility index (in %)	92	92	96	92

- *Nb. of females cycling normally and cycle length:* mean days from estrous to estrous: 4.1, 4.0, 4.1 and 4.9 days, resp. at 0, 20, 100 and 300 mg/kg bw/d (HCD (oct 2000 – Jan 2002): 3.8 – 5.4 days)

- *Female reproduction data:*

Table 21: Female reproduction data

Dose level (in mg/kg bw/d)		0	20	100	300
Nb of females		25	25	24	25
Nb of females mated		25	25	24	25
Mating day until DPC 0	Mean	2.8	2.9	2.5	3.0
	D 1 to 4	23	25	23	23
	D 5 to 8	1	0	1	0
	D 9 to 14	1	0	0	2
	D 15 to 21	0	0	0	0
Nb of females pregnant		23	23	23	23
Female fertility index (in %)		92	92	96	92

- *Duration of gestation (calculated from day 0 of pregnancy):* 22.2, 22.0, 22.2 and 22.3 days, resp. at 0, 20, 100 and 300 mg/kg bw/d.
- *Nb. of implantations, corpora lutea, litter size:* information not available
- *Nb. of pre- and post-implantation loss:* information not available
- *Nb. of dams with abortions, early deliveries, stillbirths, resorptions and/or dead fetuses:*
    - *Nb. of females with liveborn pups (gestation index):* 21 (91 %), 23 (100 %), 23 (100 %) and 21 (91 %) females, resp. at 0, 20, 100 and 300 mg/kg bw/day.
    - *Nb. of females with stillborn pups:* 3, 4, 1 and 6 females, resp. at 0, 20, 100 and 300 mg/kg bw/d (1 female of the control group and 2 females of the highest dose had all stillborn pups).
- *Nb. of live births:*

Table 22: Number of pups

Dose level (in mg/kg bw/d)	0	20	100	300
Mean nb of pups delivered	10.5	10.6	9.1	8.0*
Tot nb of pups	231	243	209	183
Nb of liveborn pups	228	239	208	173*
Live birth index (in %)	99	98	100	95
Nb of stillborn pups	3	4	1	10*

- *Data on functional observations:* /
- *Necropsy findings:* no treatment-related effects
- *Organ weight:*

Table 23: Organ weight data (in mg, g or %)

		Males				Females			
Dose level (in mg/kg bw/d)		0	20	100	300	0	20	100	300
FBW (g)		435.904	434.368	431.667	395.304*	239.146	236.408	237.625	226.05
Adrenal glands (mg)	Abs	56.56	56.32	58.333	66.92**	73.583	75.56	75.292	85.25
	Rela	0.013	0.013	0.014	0.017**	0.031	0.032	0.032	0.038**

Brain (g)	Abs	2.072	2.095	2.076	2.073	1.906	1.931	1.92	1.92
	Rela	0.48	0.487	0.483	0.529**	0.802	0.819	0.809	0.853**
Kidneys (g)	Abs	2.483	2.515	2.543	2.888**	1.749	1.768	1.803	1.805
	Rela	0.571	0.582	0.59	0.732**	0.734	0.749	0.759	0.8**
Liver (g)	Abs	10.143	10.209	10.362	10.306	6.617	6.722	6.706	6.429
	Rela	2.327	2.351	2.4	2.604**	2.766	2.841	2.821	2.835
Pituitary gland (mg)	Abs	9.68	9.64	10.083	10.04	13.208	12.64	14.083	18.917
	Rela	0.002	0.002	0.002	0.003**	0.006	0.005	0.006	0.008
Spleen (g)	Abs	0.75	0.747	0.713	0.746	0.537	0.54	0.578	0.515
	Rela	0.173	0.173	0.166	0.189*	0.226	0.229	0.244	0.229
Thyroid glands (mg)	Abs	22.44	21.88	21.542	21.68	16.5	15.64	15.167	17.5
	Rela	0.005	0.005	0.005	0.006	0.007	0.007	0.006	0.008
Cauda epididymis (g)	Abs	0.473	0.456	0.463	0.427	-	-	-	-
	Rela	0.109	0.105	0.108	0.108	-	-	-	-
Epididymides (g)	Abs	1.192	1.173	1.161	1.102	-	-	-	-
	Rela	0.275	0.272	0.27	0.279	-	-	-	-
Prostate (g)	Abs	1.135	1.078	1.025	0.774**	-	-	-	-
	Rela	0.263	0.249	0.239	0.253	-	-	-	-
Seminal vesicle (g)	Abs	1.002	0.999	1.025	0.997	-	-	-	-
	Rela	0.231	0.232	0.239	0.196*	-	-	-	-
Testes (g)	Abs	3.806	3.827	3.686	3.735	-	-	-	-
	Rela	0.876	0.887	0.859	0.947*	-	-	-	-
Ovaries (mg)	Abs	-	-	-	-	105.917	103.28	113.125	93.792*
	Rela	-	-	-	-	0.045	0.044	0.048	0.042
Uterus (g)	Abs	-	-	-	-	0.718	0.732	0.648	0.702
	Rela	-	-	-	-	0.302	0.31	0.273	0.314

- *Histopathological findings:*

Table 24: Incidence of microscopic findings

		Males				Females			
Dose level (in mg/kg bw/d)		0	20	100	300	0	20	100	300
Adrenal cortex									
Nb animals examined		25	2	2	25	25	2	2	25
Diffuse hypertrophy		0	0	0	20 (grade 2)	0	0	0	20 (grade 1)
Kidneys									
Nb animals examined		25	3	2	25	25	2	2	25
Calcification, medulla		1	0	0	0	6	0	0	11
Calcification, pelvis		3	0	0	4	10	1	0	11
Calcification, papilla		2	0	0	0	2	0	0	1
Nephropathy		4	0	0	7	4	0	1	7
Eosinophilic droplets	Inc	4	0	0	9	0	0	0	0
	Grade 1	4	-	-	5	-	-	-	-
	Grade 2	-	-	-	4	-	-	-	-
Liver									
Nb animals examined		25	2	2	25	0	1	0	1
Focal necrosis		1	0	0	1	-	-	-	-
Central hypertrophy	inc	0	0	0	23	-	-	-	-
	Grade 1	-	-	-	17	-	-	-	-
	Grade 2	-	-	-	6	-	-	-	-

Spleen								
Nb animals examined	25	2	2	25	-	-	-	-
Hematopoiesis	20	1	1	22	-	-	-	-
Epididymis, left								
Nb animals examined	25	2	2	25	-	-	-	-
Lymphoid infiltr.	2	0	0	4	-	-	-	-
Testes, left								
Nb animals examined	25	2	2	25	-	-	-	-
Degeneration, focal	3	0	1	3	-	-	-	-
Degeneration, diffus	0	0	0	1	-	-	-	-
Prostate								
Nb animals examined	25	2	2	25	-	-	-	-
Inflamm. chronic	7	0	0	7	-	-	-	-
Uterus								
Nb animals examined	-	-	-	-	25	2	2	25
Dilation of horn(s)	-	-	-	-	9	1	0	4

- *Body weight change and gravid uterine weight, including optionally, body weight change corrected for gravid uterine weight:* /

For F1 pups/litters (per dose): F1B pups

- *Mean number of live pups (litter size):*

Table 25: Number of pups

Dose level (in mg/kg bw/d)	0	20	100	300
Mean nb of pups delivered	10.5	10.6	9.1	8.0*
Tot nb of pups	231	243	209	183
Nb of liveborn pups	228	239	209	173*
Nb of stillborn pups	3	4	1	10*
Nb of pups died	0	2	0	6**
Nb of pups cannibalized	1	1	2	14**

- *Litter data:*

Table 26: Litter data (mean nb of pups)

Dose level (in mg/kg bw/d)	0	20	100	300
PND 1	10.3	10.3	9.0	6.9
PND 4 (preculling)	10.3	10.3	9.0	6.7
PND 4 (postculling)	7.6	7.6	6.8	5.8
PND 7	7.6	7.6	6.8	5.8
PND 14	7.6	7.6	6.8	5.7
PND 21	7.6	7.6	6.8	5.7

- *Sex ratio:*
    - *At day 0:* 51.8/48.2, 44.4/55.6, 46.6/53.6 and 50.3/49.7 % of live males/females, resp. at 0, 20, 100 and 300 mg/kg bw/d.

- *At day 21:* 50.6/49.4, 46.3/53.7, 49.4/50.6 and 49.2/50.8 % of live males/females, resp. at 0, 20, 100 and 300 mg/kg bw/d.

- *Mortality:*

Table 27: Mortality data

Dose level (in mg/kg bw/d)	0	20	100	300
At D 0	0	0	0	2
Between D 1 to 4	1	3	1	16
Between D 5 to 7	0	0	0	1
Between D 8 to 14	0	0	1	1
Between D 15 to 21	0	0	0	0

- *Viability index (pups surviving 4 days/total births):* 100, 99, 100 and 90 %, resp. at 0, 20, 100 and 300 mg/kg bw/d (pups surviving between D 0 to 4: 227, 236, 207 and 155**, resp. at 0, 20, 100 and 300 mg/kg bw/d). (HCD range: 96 to 100 %)
- *Survival index at weaning:* 100, 100, 99 and 99 %, resp. at 0, 20, 100 and 300 mg/kg bw/d (pups surviving between D 4 to 21: 168, 175, 156 and 132, resp. at 0, 20, 100 and 300 mg/kg bw/d).
- *Mean litter or pup weight by sex and with sexes combined:*

Table 28: Mean pups body weight (in g)

Dose level (in mg/kg bw/d)		0	20	100	300	HCD range
PND 1	M	6.4	6.6	6.9	6.4	4.9 – 8.5
	F	6.1	6.3	6.5	6.0	4.5 – 7.9
	M+F	6.3	6.4	6.7	6.1	4.7 – 7.9
PND 4 (preculling)	M	9.6	10.1	10.8*	9.4	
	F	9.4	9.7	10.2	9.2	
	M+F	9.5	9.9	10.5	9.3	
PND 4 (postculling)	M	9.6	10.1	10.8*	9.5	
	F	9.5	9.8	10.2	9.2	
	M+F	9.6	9.9	10.5	9.3	
PND 7	M	15.0	16.0	16.5*	13.8	8.6 – 19.9
	F	14.9	15.5	15.9	13.8	6.7 – 18.7
	M+F	14.9	15.7	16.1	13.9	7.3 – 19.0
PND 14	M	30.0	32.1	32.4	28.3	15.3 – 38.8
	F	29.6	31.5	31.7	28.1	10.1 – 36.5
	M+F	29.8	31.8	31.9	28.2	12.7 – 37.3
PND 21	M	47.1	51.1*	51.2*	45.5	22.9 – 61.9
	F	46.3	49.6	49.8	44.6	17.7 – 58.3
	M+F	46.7	50.2*	50.4*	44.9	20.3 – 60.1

- *Body weight change:*

Table 29: Mean pups body weight change (in g)

Dose level (in mg/kg bw/d)		0	20	100	300
D 1 to 4	M	3.3	3.5	3.8*	3.1

	F	3.3	3.4	3.7	3.2
	M+F	3.3	3.4	3.7	3.2
D 4 to 21	M	37.4	41.0*	40.4	36.0
	F	36.9	39.9*	39.6	35.4
	M+F	37.2	40.4*	39.9	35.6

- *Necropsy observation:*
  - *Total nb of pups with necropsy findings:* 7, 2, 3 and 9 pups, resp. at 0, 20, 100 and 500 mg/kg bw/d.
  - *Litter incidence:* 5, 2, 3 and 8, resp. at 0, 20, 100 and 500 mg/kg bw/d.
  - *Mean % of affected pups/litter:* 3.3, 0.9, 1.1 and 5.8 %, resp. at 0, 20, 100 and 500 mg/kg bw/d.
- *Pups organ weight data:*

Table 30: Pups organ weight (in g or %)

Dose level (in mg/kg bw/d)		0	20	100	300	HCD range (Oct 00 – Jun 02)
Brain	Abs	1.451	1.494**	1.497**	1.458	0.888 – 1.697
	Rela	3.119	2.983*	2.992	3.359*	1.773 – 5.821
Thymus	Abs	0.221	0.234	0.233	0.212	0.042 – 0.322
	Rela	0.472	0.466	0.463	0.482	0.198 – 0.662
Spleen	Abs	0.211	0.243**	0.239**	0.195	0.303 – 0.538
	Rela	0.451	0.487	0.485	0.453	0.136 – 0.741

HCD: 19 studies during period 05/00 to 11/02 with Wistar rat

- *External, soft tissue and skeletal malformations and other relevant alterations:* /
- *Nb. and percent of fetuses and litters with malformations (including runts) and/or variations as well as description and incidences of malformations and main variations (and/or retardations):* /
- *Data on physical landmarks in pups and other postnatal developmental data:* /
- *Vaginal opening:*

Table 31: Sexual maturation data: vaginal opening

Dose level (in mg/kg bw/d)	0	20	100	300	HCD range
Nb pups tested	25	25	25	25	
Mean days to criterion	31.8	31.0	30.2**	30.7	30.8 – 33.8
Mean bw at criteria (in g)	92.2	92.3	89.9	84.6	86.2 – 97.8

HCD: 9 studies with Wistar rats during the period 03/00 to 03/02

- *Preputial separation:*

Table 32: Sexual maturation: preputial separation

Dose level (in mg/kg bw/d)	0	20	100	300	HCD range
Nb pups tested	25	25	25	25	
Mean days to criterion	43.3	43.3	43.1	43.8	42.5 – 45.0
Mean bw at criteria (in g)	169.5	180.0	178.8	168.7	164.8 – 180.6

HCD: 9 studies with Wistar rats during the period 03/00 to 03/02

For F1 adults (per dose): F1M and F1F parents

- *Actual dose received by dose level by sex if known:*

Table 33: Mean actual test substance intake (in mg/kg bw/d)

		Low dose	Mid dose	High dose
Males				
W 0 to 18		20.7	103.1	307.0
Females				
Premating period	W 0 to 10	21.1	105.5	317.2
Gestation period	D 0 to 20	20.1	101.1	305.1
Lactation period	D 1 to 14	17.6	90.1	262.8

- *Nb. of animals at the start of the test:* 25/sex/dose
- *Mortality:* one female of the control group was sacrificed during the study week 8 (this female had only half of the bw of the other control females, had still not opened its vagina and did not develop upper incisive. Necropsy revealed distinct atrophy of ovary, oviducts and uterus.). Moreover, one female of the lowest dose group had to be sacrificed in a moribund state during study week 10 (poor general state, apathy, piloerection and red crust formation at its nose. Necropsy revealed a severe chronic progressive nephropathy).
- *Clinical observations:* no treatment-related effect was observed.
- *Mean food consumption:*
    - *In males:* W 0 to 17: 21.8, 22.3, 22.1 and 20.9 g/animal/day, resp. at 0, 20, 100 and 500 mg/kg bw/d.
    - *In females:* premating period: W 0 to 10: 16.4, 17.0, 17.1 and 16.3 g/animal/day, resp. at 0, 20, 100 and 500 mg/kg bw/d.

      Gestation period: days 0 to 20: 20.9, 20.9, 21.2 and 19.4 g/animal/day, resp. at 0, 20, 100 and 500 mg/kg bw/d.

      Lactation period: days 1 to 14: 37.5, 37.2, 38.2 and 33.7 g/animal/day, resp. at 0, 20, 100 and 500 mg/kg bw/d.
- *Body weight data:*

Table 34: Body weight in males (in g)

Dose level (in mg/kg bw/d)	0	20	100	300
W 1	71.4	75.5	78.0	69.7
W 5	258.5	272.5	271.1	258.9
W 10	345.4	365.6	359.5	343.7
W 14	378.8	394.5	386.5	367.2
W 17	397.7	414.9	407.9	384.0
BWG (W 0 to 17)	326.2	339.4	330.0	314.3

Table 35: Body weight data in females (in g)

Dose level (in mg/kg bw/d)		0	20	100	300
Premating period	W 0	66.8	68.9	72.4	66.8
	W 5	166.8	173.4	178.6	173.8
	W 10	210.9	212.1	219.3	211.0
	BWG (W 0 to 10)	142.7	143.1	146.9	144.1
Gestation period	D 0	215.6	217.5	222.1	215.0
	D 7	238.9	241.3	246.7	233.3
	D 14	260.3	262.3	268.9	252.5
	D 20	308.5	310.2	318.3	301.2
	BWG (D 0 to 20)	92.9	92.7	96.2	86.1
Lactation period	D 1	238.6	242.9	247.8	236.2
	D 4	249.3	251.9	258.0	244.6
	D 14	267.9	270.9	276.3	262.9
	D 21	250.3	263.1	271.4	262.1
	BWG (D 1 to 21)	21.7	20.2	23.6	25.9

- *Haematological and clinical biochemistry findings:*

Table 36: Biological data

	Males				Females			
Dose level (in mg/kg bw/d)	0	20	100	300	0	20	100	300
ALT (µkat/L)	0.75	0.68	0.81	0.85**	0.70	0.65	0.60*	0.61*
AST (µkat/L)	2.56	2.17	2.45	2.52	2.24	2.13	191	2.03
ALP (µkat/L)	1.18	1.21	1.18	1.15	0.71	0.72	0.71	0.74
SGGT (nkat/L)	5	3	6	5	9	7	7	9
GLDH (nkat/L)	140	173*	209**	236**	130	97	129	191**
Tot. prot. (g/L)	70.81	70.19	71.15	71.08	68.0	68.67	68.12	70.47
Chol (mmol/L)	2.03	2.12	2.27*	2.92**	1.52	1.38	1.37	1.84**

- *Hormones:*

Table 37: Hormone analysis

	Males				Females			
Dose level (in mg/kg bw/d)	0	20	100	300	0	20	100	300
ALD (pmol/L)	711.55	658.71	538.38*	561.86	1953.93	1894.92	1857.95	1305.03**
CC (nmol/L)	776.36	588.61	526.70	664.15	2508.74	2313.71	2258.12	1970.37*
T (nmol/L)	7.57	7.17	3.33*	3.28	1.26	1.24	1.10	0.81*
LH (µg/L)	1.26	0.99	0.97	1.08	20.29	15.49	35.53	21.12
FSH (µg/L)	11.68	11.97	12.00	11.79	10.89	9.87	10.27	13.24
E_2 (pmol/L)	-	-	-	-	199.67	179.39	142.99*	106.97**

- *Effects on sperm:*

Table 38: Sperm evaluation

Dose level (in mg/kg bw/d)	0	20	100	300	HCD range

Mean tot spermatids/g testis	121	NT	NT	125	94 - 144
Mean tot sperm/g cauda epididyma	594	NT	NT	532	517 – 727
Mean % normal sperm	98.0	NT	NT	95.7	94.8 – 99.1
Mean % abnormal sperm	2.0	NT	NT	4.3	0.9 – 5.2
Mean % motility	84	82	86	77	81 - 92

HCD: from 03/00 to 03/02 (16 studies during this period – Wistar rat)

- *Cohabitation data:*

Table 39: Male cohabitation data

Dose level (in mg/kg bw/d)	0	20	100	300
Nb of males placed with females	24	24	25	25
Nb of males mated	24	24	25	22
Nb of males with females pregnant	22	24	25	20
Male fertility index (in %)	92	100	100	80

- *Nb. of females cycling normally and cycle length:*
  - *Mean of days from estrous to estrous:* 3.9, 4.3, 3.9 and 4.2 days, resp. at 0, 20, 100 and 300 mg/kg bw/d (HCD (oct 2000 – Jan 2002): 3.8 – 5.4 days)
- *Female reproduction data:*

Table 40: Female reproduction data

Dose level (in mg/kg bw/d)		0	20	100	300
Nb of females		24	24	25	25
Nb of females mated		24	24	24	22
Mating day until DPC 0	Mean	2.1	2.0	2.5	3.1*
	D 1 to 4	24	24	25	19
	D 5 to 8	0	0	0	3
	D 9 to 14	0	0	0	0
	D 15 to 21	0	0	0	0
Nb of females pregnant		22	24	25	20
Female fertility index (in %)		92	100	100	91

- *Duration of gestation (calculated from day 0 of pregnancy):* 21.5, 21.5, 21.8 and 22.0* days, resp. at 0, 20, 100 and 300 mg/kg bw/d.
- *Nb. of implantations, corpora lutea, litter size:*
  - *Mean nb of implantation sites:* 10.6, 10.7, 12.2* and 10.5, resp. at 0, 20, 100 and 300 mg/kg bw/d.
- *Nb. of pre- and post-implantation loss:*
  - *Post-implantation loss:* mean nb: 0.5, 0.7, 1.4 and 0.9, resp. at 0, 20, 100 and 300 mg/kg bw/d) (percentage of post-implantation loss: 7.8, 6.3, 10.5 and 8.4 %, resp. at 0, 20, 100 and 300 mg/kg bw/d)
- *Nb. of dams with abortions, early deliveries, stillbirths, resorptions and/or dead fetuses:*

- *Nb. of females with liveborn pups (gestation index):* 21 (95 %), 24 (100 %), 25 (100 %) and 20 (100 %) females, resp. at 0, 20, 100 and 300 mg/kg bw/day.
- *Nb. of females with stillborn pups:* 2, 1, 1 and 7 females, resp. at 0, 20, 100 and 300 mg/kg bw/d (no female with all stillborn).

- *Nb. of live births:*

Table 41: Number of pups

Dose level (in mg/kg bw/d)	0	20	100	300
Mean nb of pups delivered	10.6	10.0	10.8	9.6
Tot nb of pups	223	240	269	191
Nb of liveborn pups	220	239	268	176**
Live birth index (in %)	99	100	100	92
Nb of stillborn pups	3	1	1	15**

- *Data on functional observations:* /
- *Necropsy findings:* no treatment-related findings observed.
- *Organ weight:*

Table 42: Organ weight data (in mg, g or %)

		Males				Females			
Dose level (in mg/kg bw/d)		0	20	100	300	0	20	100	300
FBW (g)		370.436	389.084	380.352	358.144	220.525	222.338	225.888	217.508
Adrenal glands (mg)	Abs	63.36	62.2	65.04	72.96**	76.375	74.083	83.2*	87.28**
	Rela	0.017	0.016	0.017	0.02**	0.035	0.033	0.037	0.04*
Brain (g)	Abs	2.012	2.052	2.07	2.041	1.925	1.921	1.939	1.937
	Rela	0.551	0.532	0.547	0.573	0.878	0.867	0.862	0.895
Kidneys (g)	Abs	2.259	2.292	2.346	2.526**	1.546	1.54	1.591	1.568
	Rela	0.613	0.591	0.618	0.707**	0.702	0.693	0.706	0.722
Liver (g)	Abs	8.758	9.333	9.33	9.47	5.744	5.818	6.071	6.036
	Rela	2.368	2.392	2.451*	2.644**	2.604	2.618	2.694	2.776**
Pituitary gland (mg)	Abs	10.08	10.52	10.28	10.24	12.75	13.0	12.84	12.76
	Rela	0.003	0.003	0.003	0.003	0.006	0.006	0.006	0.006
Spleen (g)	Abs	0.661	0.654	0.645	0.685	0.504	0.484	0.52	0.512
	Rela	0.181	0.169	0.17	0.191*	0.229	0.217	0.231	0.236
Thyroid glands (mg)	Abs	21.48	20.36	20.24	20.8	16.958	16.042	16.96	15.64
	Rela	0.006	0.005*	0.005	0.006	0.008	0.007	0.008	0.007
Cauda epididymis (g)	Abs	0.461	0.458	0.465	0.452	-	-	-	-
	Rela	0.125	0.118	0.123	0.127	-	-	-	-
Epididymides (g)	Abs	1.162	1.16	1.151	1.122	-	-	-	-
	Rela	0.316	0.3	0.304	0.314	-	-	-	-
Prostate (g)	Abs	0.992	0.996	0.968	0.983	-	-	-	-
	Rela	0.271	0.258	0.256	0.275	-	-	-	-
Seminal vesicle (g)	Abs	1.061	1.018	1.0	0.904**	-	-	-	-
	Rela	0.29	0.262	0.264	0.254	-	-	-	-
Testes (g)	Abs	3.716	3.856	3.738	3.56	-	-	-	-
	Rela	1.012	1.0	0.986	0.997	-	-	-	-
Ovaries (mg)	Abs	-	-	-	-	107.75	168.833[A]	119.36*	102.8

	Rela	-	-	-	-	0.049	0.075	0.053	0.047
Uterus (g)	Abs	-	-	-	-	0.6	0.608	0.677	0.695
	Rela	-	-	-	-	0.273	0.274	0.301	0.318

[A]: St. Dev.: 289.166

- *Histopathological findings:*

Table 43: Microscopic findings

		Males				Females			
Dose level (in mg/kg bw/d)		0	20	100	300	0	20	100	300
Adrenal cortex									
Nb animals examined		25	1	0	25	25	1	1	25
Diffuse hypertrophy	Inc	0	0	-	18	0	0	0	21
	Grade 1	-	-	-	18	-	-	-	18
	Grade 2	-	-	-	0	-	-	-	3
Kidneys									
Nb animals examined		25	25	25	25	0	1	0	0
Calcification, pelvis	Inc	0	0	0	1	-	0	-	-
Nephropathy	Inc	5	1	0	8	-	1	-	-
Eosinophilic droplets	Inc	23	25	23	25	-	0	-	-
	Grade 1	7	13	12	-	-	-	-	-
	Grade 2	15	11	11	7	-	-	-	-
	Grade 3	1	1	-	18	-	-	-	-
Liver									
Nb animals examined		25	0	0	25	25	0	1	25
Central hypertrophy	Inc	0	-	-	18	0	-	0	16
	Grade 1	-	-	-	10	-	-	-	16
	Grade 2	-	-	-	8	-	-	-	-
Spleen									
Nb animals examined		25	0	0	25	0	0	0	0
Hematopoiesis	Inc	20	-	-	19	-	-	-	-
Epididymis, left									
Nb animals examined		25	0	1	25	-	-	-	-
Lymphoid infiltr	Inc	3	-	1	3	-	-	-	-
Testes, left									
Nb animals examined		25	0	1	25	-	-	-	-
Degeneration, focal	Inc	1	-	0	1	-	-	-	-
Uterus									
Nb animals examined		-	-	-	-	25	1	0	25
Dilatation of horn(s)	Inc	-	-	-	-	4	0	-	11
Atrophy	Inc	-	-	-	-	1	1	-	3

- *Body weight change and gravid uterine weight, including optionally, body weight change corrected for gravid uterine weight: /*
- *Differential ovarian follicle count:*

Table 44: Abs and mean values of differential ovarian follicle count

Dose level (in mg/kg bw/d)		0	300
Primordial	Abs values	6.525	7.264
	Mean values	271.9	290.6
Growing	Abs values	859	922
	Mean values	35.8	36.9
Primordial + growing	Abs values	7.384	8.186
	Mean values	307.7	327.4

For F2 pups/litters (per dose): F2 pups

- *Mean number of live pups (litter size):*

Table 45: Number of pups

Dose level (in mg/kg bw/d)	0	20	100	300
Mean nb of pups delivered	10.6	10.0	10.8	9.6
Tot nb of pups	223	240	269	191
Nb of liveborn pups	220	239	268	176**
Nb of stillborn pups	3	1	1	15**
Nb of pups died	2	2	3	13**
Nb of pups cannibalized	0	3	1	6**

- *Litter data:*

Table 46: Litter data (mean nb of pups)

Dose level (in mg/kg bw/d)	0	20	100	300
PND 1	10.4	9.8	10.6	7.8
PND 4 (preculling)	10.4	9.8	10.6	7.8
PND 4 (postculling)	7.9	7.8	8.0	6.8
PND 7	7.9	7.8	7.9	6.8
PND 14	7.9	7.8	7.9	6.8
PND 21	7.9	7.8	7.9	6.8

- *Sex ratio:*
    - *At day 0:* 50.5/49.5, 45.6/54.4, 47.8/52.2 and 52.8/47.2 % of males/% of females, resp. at 0, 20, 100 and 300 mg/kg bw/d.
    - *At day 21:* 50.3/49.7, 47.8/52.2, 50.8/49.2 and 54.8/45.2 % of males/% of females, resp. at 0, 20, 100 and 300 mg/kg bw/d.
- *Mortality:*

Table 47: Mortality data

Dose level (in mg/kg bw/d)	0	20	100	300
At D 0	0	1	2	4
D 1 to 4	2	4	0	15
D 5 to 7	0	0	1	0
D 8 to 14	0	0	1	0
D 15 to 21	0	0	0	0

- *Viability index (pups surviving 4 days/total births):* 99, 98, 99 and 89 %, resp. at 0, 20, 100 and 300 mg/kg bw/d (pups surviving D 0 to 4: 218, 234, 266 and 157**, resp. at 0, 20, 100 and 300 mg/kg bw/d).
- *Survival index at weaning:* 100, 100, 99 and 100 %, resp. at 0, 20, 100 and 300 mg/kg bw/d (pups surviving D 4 to 21: 165, 186, 197 and 135, resp. at 0, 20, 100 and 300 mg/kg bw/d).
- *Mean litter or pup weight by sex and with sexes combined:*

Table 48: Mean pups body weight (in g)

Dose level (in mg/kg bw/d)		0	20	100	300	HCD range
PND 1	M	6.0	6.3	6.3	6.0	4.9 – 8.5
	F	5.7	6.0	6.0	5.8	4.5 – 7.9
	M+F	5.8	6.1	6.2	5.9	4.7 – 7.9
PND 4 (preculling)	M	9.2	9.6	9.4	9.4	
	F	8.8	9.4	9.1	9.2	
	M+F	9.0	9.5	9.2	9.3	
PND 4 (postculling)	M	9.2	9.7	9.5	9.4	
	F	8.9	9.4	9.1	9.2	
	M+F	9.1	9.5	9.3	9.3	
PND 7	M	14.9	15.2	15.0	14.7	8.6 – 19.9
	F	14.6	14.8	14.5	14.5	6.7 – 18.7
	M+F	14.7	14.9	14.8	14.6	7.3 – 19.0
PND 14	M	29.7	30.1	29.5	29.5	15.3 – 38.8
	F	29.4	29.3	28.7	29.3	10.1 – 36.5
	M+F	29.6	29.6	29.1	29.4	12.7 – 37.3
PND 21	M	46.5	47.5	47.3	47.3	22.9 – 61.9
	F	45.9	46.1	45.7	46.7	17.7 – 58.3
	M+F	46.3	46.7	46.5	47.0	20.3 – 60.1

- *Body weight change:*

Table 49: Mean pups body weight change (in g)

Dose level (in mg/kg bw/d)		0	20	100	500
D 1 to 4	M	3.2	3.3	3.1	3.4
	F	3.2	3.3	3.1	3.4
	M+F	3.2	3.3	3.1	3.4
D 4 to 21	M	37.4	37.9	37.9	37.9
	F	37.1	36.7	36.6	37.5
	M+F	37.3	37.2	37.3	37.7

- *Necropsy observations:*
    - *Total nb. of pups with necropsy findings:* 1, 1, 1 and 3 pups, resp. at 0, 20, 100 and 500 mg/kg bw/d.
    - *Litter incidence:* 1, 1, 1 and 3, resp. at 0, 20, 100 and 500 mg/kg bw/d.

- *Mean % of affected pups/litter:* 0.5, 0.3, 0.6 and 3.0 %, resp. at 0, 20, 100 and 500 mg/kg bw/d.

- *Pups organ weight data:*

Table 50: Pups organ weight (in g or %)

Dose level (in mg/kg bw/d)		0	20	100	300	HCD range
Brain	Abs	1.465	1.479	1.479	1.493	0.888 – 1.697
	Rela	3.171	3.165	3.203	3.202	1.773 – 5.821
Thymus	Abs	0.222	0.217	0.224	0.222	0.042 – 0.322
	Rela	0.479	0.462	0.483	0.471	0.198 – 0.662
Spleen	Abs	0.218	0.225	0.220	0.225	0.303 – 0.538
	Rela	0.479	0.473	0.471	0.474	0.136 – 0.741

HCD: 19 studies during period 05/00 to 11/02 with Wistar rat

- *External, soft tissue and skeletal malformations and other relevant alterations:* /
- *Nb. and percent of fetuses and litters with malformations (including runts) and/or variations as well as description and incidences of malformations and main variations (and/or retardations):* /
- *Data on physical landmarks in pups and other postnatal developmental data:* /
- *Data on functional observations:* /

3.10.1.2 Pre- and postnatal developmental toxicity study in Wistar rats (range-finding study) (Anonymous, 2013)

Study reference

Anonymous, 2013

Detailed study summary and results

Test type

OECD TG 416

GLP

Test substance

- DMPP
- *Purity:* 99.4 g/100 g

Test animals

- *Species/strain/sex:* Rat / Wistar / female
- *Nb of animals per sex per dose:* 25 pregnant females/dose
- *Age and weight at the study initiation:* bw at GD 0 was between 139.6 to 192.0 g

Administration/exposure

- *Route of administration:* oral, diet
- *Duration and frequency of test/exposure period:* GD 6 until weaning, daily
- *Doses/concentration levels, rationale for dose level selection:* 0, 20, 100 and 300 mg/kg bw/d

- *Vehicle:* / (diet only)

Description of test design:

- *Details on mating procedure (M/F ratios per cage, length of cohabitation, proof of pregnancy):* /
- *Premating exposure period for males and females (P and F1):* /
- *Standardization of litters (yes/no and if yes, how and when):* on PND 4 (4 pups/sex/litter)

Results and discussion

- *Actual dose received by dose level by sex if known:*

Table 51: Mean maternal substance intake

Dose level (in mg/kg bw/d)	0	20	100	300
Gestation period (GD 6-20)	0	20.4	104.5	302.7
Lactation period (LD 1-21)	0	19.8	98.6	293.6

For Parental generation (per dose):

- *Time of death during the study and whether animals survived to termination:* no mortality occurred during the study period
- *Clinical observations:* no treatment-related findings
- *Food consumption:*

Table 52: Food consumption (in g/animal/day)

Dose level (in mg/kg bw/d)		0	20	100	300
Gestation period	0-6	17.1	16.6	17.0	17.4
	6-13	20.0	19.3	19.7	17.4**
	13-20	20.7	20.4	21.5	21.7
	GD 0 to 20	19.2	18.7	19.4	18.8
Lactation period	1-4	31.5	30.1	31.4	29.4
	4-7	39.8	38.9	39.0	37.6
	7-14	52.2	51.2	51.2	50.1
	14-21	60.6	58.9	58.9	59.6
	LD 1 to 21	46.0	44.8	45.1	44.2

- *Body weight data:*

Table 53: Body weight (in g)

Dose level (in mg/kg bw/d)		0	20	100	300	HCD range of actual values (01/07 to 02/11)
Gestation period	GD 0	169.1	166.8	167.4	167.5	172.7 – 298.9
	GD 6	201.8	198.3	199.4	199.7	At GD 7: 188.7 – 331.3
	GD 13	231.9	226.6	231.3	222.0	At GD 14: 207.7 – 350.3
	GD 20	291.0	279.5	289.0	285.2	225.6 – 418.3
	BWG GD 0 to 20	121.9	112.7	121.6	117.7	
Lactation period	LD 1	226.1	221.0	226.1	224.0	180.8 – 331.3
	LD 4	242.2	237.8	242.6	239.0	192.7 – 348.6
	LD 7	251.1	246.0	250.2	246.5	199.5 – 338.1

	LD 14	267.7	264.7	267.1	261.5	203.5 – 358.3
	LD 21	259.2	257.0	257.8	257.1	198.3 – 329.1
	LD 1 to 21	33.1	36.0	31.7	33.2	

- *Haematological and clinical biochemistry findings:*
  - *Hormones:*

Table 54: Hormones data

Dose level (in mg/kg bw/d)	0	20	100	300
At week 2				
LH (µg/L)	1.0	1.0	1.0	1.0
FSH (µg/L)	4.21	4.16	4.31	4.26
E_2 (pmol/L)	7.4	7.36	6.27	9.75
At week 6				
LH (µg/L)	12.65	6.11	11.17	19.94
FSH (µg/L)	7.48	4.97	6.84	6.70
E_2 (pmol/L)	20.09	17.23	17.13	18.69
11-Deoxy-corticosterone (nmol/L)	41.14	23.09**	12.62**	9.48**
18-Deoxy-corticosterone (nmol/L)	186.8	137.9	118.9**	165.1
Corticosterone (nmol/L)	1776	1267	1231**	1654
Progesterone (nmol/L)	49.48	40.47	27.76**	32.92*
11-Deoxy-cortisol (nmol/L)	3.90	3.40	3.56	3.82

- *Female mating index:* 100 % in all dose groups.
- *Fertility index:* 96 (24/25), 100 (25/25), 96 (24/25) and 96 (24/25) %, resp. at 0, 20, 100 and 300 mg/kg bw/d.
- *Nb. of females cycling normally and cycle length:* /
- *Mean duration of gestation (calculated from day 0 of pregnancy):* 21.9, 22.0, 22.1 and 22.3 days, resp. at 0, 20, 100 and 300 mg/kg bw/d (HCD range values (study period: 2000 to 2011): 21.5 to 22.5 days).
- *Precoital interval (number of days until mating and number of estrous periods until mating):* /
- *Nb. of implantations, corpora lutea, litter size:*
  - *Total nb of implantation sites:* 265, 240, 238 and 242, resp. at 0, 20, 100 and 300 mg/kg bw/d.
  - *Mean nb of implantation sites:* 11.0, 9.6*, 9.9 and 10.1, resp. at 0, 20, 100 and 300 mg/kg bw/d (HCD range values (study period: 2000 to 2011): 10.2 to 13.7).
- *Post-implantation loss:*
  - *Total nb of post-implantation loss:* 14, 12, 13 and 18, resp. at 0, 20, 100 and 300 mg/kg bw/d.
  - *Mean % of post-implantation loss:* 5.4, 4.4, 6.4 and 6.8 %, resp. at 0, 20, 100 and 300 mg/kg bw/d (HCD range values: 2.5 to 17.7).
- *Nb. of dams with abortions, early deliveries, stillbirths, resorptions and/or dead fetuses:*

- One sperm positive female of the control group, one of the mid dose group and one of the highest dose did not deliver pups.
- *Nb of females with liveborn pups:* 24, 25, 23, 24 females, resp. at 0, 20, 100 and 300 mg/kg bw/d.
- *Nb of females with stillborn pups:* 0, 1, 1 and 2 females, resp. at 0, 20, 100 and 300 mg/kg bw/d (at the mid dose the female had all stillborn pups).

- *Nb. of live births:*

Table 55: Live births data

Dose level (in mg/kg bw/d)	0	20	100	300	HCD range
Tot nb of pups delivered	251	228	225	224	
Mean nb of pups delivered	10.5	9.1	9.4	9.3	9.3 – 12.8
Tot. nb of liveborn pups	251	227	223	221	
Nb of stillborn pups	0	1	2	3	0 - 7

- *Necropsy findings:* no treatment-related abnormalities observed (no abnormalities in 20, 20, 21 and 20 females, resp. at 0, 20, 100 and 300 mg/kg bw/d).
- *Body weight at sacrifice and absolute and relative organ weight data for the parental animals:*

Table 56: Organ weight data (in mg or g and %)

Dose level (in mg/kg bw/d)		0	20	100	300
FBW (g)		212.392	209.748	214.008	212.55
Adrenal glands (mg)	Abs	83.125	85.76	91.0*	95.833
	Rela	0.039	0.041	0.043*	0.045**
Brain (g)	Abs	1.836	1.866	1.862	1.854
	Rela	0.867	0.892	0.871	0.875
Kidneys (g)	Abs	1.821	1.803	1.877	1.832
	Rela	0.859	0.862	0.878	0.864
Liver (g)	Abs	6.986	6.95	7.439	6.951
	Rela	3.294	3.322	3.479	3.282
Pituitary gland (mg)	Abs	11.417	10.76	11.042	10.708
	Rela	0.005	0.005	0.005	0.005
Spleen (g)	Abs	0.465	0.467	0.48	0.458
	Rela	0.219	0.223	0.225	0.216
Thyroid glands (mg)	Abs	16.875	16.36	16.542	17.853
	Rela	0.008	0.008	0.008	0.008
Ovaries (mg)	Abs	114.417	112.4	112.75	108.375
	Rela	0.054	0.054	0.053	0.051
Uterus (g)	Abs	0.564	0.589	0.616	0.57
	Rela	0.266	0.282	0.287	0.27

- *Histopathological findings:* no histopathological investigation was carried out.

For F1 pups/litters (per dose):

- *Mean number of live pups (litter size):*

Table 57: Litter data

Dose level (in mg/kg bw/d)	0	20	100	300	HCD range
Tot. nb of pups delivered	215	228	225	224	
Mean nb of pups delivered	10.5	9.1	9.4	9.3	9.3 – 12.8
Tot. nb of liveborn pups	251	227	223	221	
Nb of stillborn pups	0	1	2	3	0 - 7

- *Sex ratio:*
  - *At D 0:* 52.2, 47.1, 46.6 and 44.3 % of males, resp. at 0, 20, 100 and 300 mg/kg bw/d.
  - *At D 21:* 52.7, 49.2, 49.4 and 47.5 % of males, resp. at 0, 20, 100 and 300 mg/kg bw/d.
- *Pups dead:*

Table 58: Pups mortality

Dose level (in mg/kg bw/d)	0	20	100	300
At D 0	0	1	1	2
D 1 to 4	2	1	2	16
D 5 to 7	1	0	0	0
D 8 to 14	0	0	0	0
D 15 to 21	0	0	0	0

  - *Nb of pups cannibalized:* 2, 2, 3 and 16** pups, resp. at 0, 20, 100 and 300 mg/kg bw/d.
- *Viability index (pups surviving 4 days/total births):* 99 (249 pups), 99 (225 pups), 99 (220 pups) and 92 % (203** pups), resp. at 0, 20, 100 and 300 mg/kg bw/d (HCD range (2000-2009): 94 to 100 %).
- *Survival index at weaning:* 99 (188 pups), 100 (189 pups), 100 (174 pups) and 100 % (179 pups), resp. at 0, 20, 100 and 300 mg/kg bw/d (HCD range: 95 to 100 %).
- *Litter data:*

Table 59: Mean nb of live pups/litter

Dose level (in mg/kg bw/d)	0	20	100	300
PND 1	10.4	9.0	9.2	8.6
PND 4 (preculling)	10.4	9.0	9.2	8.5
PND 4 (postculling)	7.9	7.6	7.3	7.5
PND 7	7.8	7.6	7.3	7.5
PND 14	7.8	7.6	7.3	7.5
PND 21	7.8	7.6	7.3	7.5

- *Mean litter or pup weight by sex and with sexes combined:*

Table 60: Pups body weight data (in g)

Dose level (in mg/kg bw/d)		0	20	100	300	HCD range of study means
PND 1	M	6.8	7.1	7.4**	7.1	5.9 – 7.0
	F	6.5	6.8	7.1**	6.8	5.7 – 6.7
	M + F	6.7	6.9	7.3**	7.0	5.8 – 6.9

PND 4 (pre-culling)	M	10.5	10.8	11.6**	11.1	
	F	10.1	10.4	11.1*	10.6	
	M + F	10.4	10.6	11.3*	10.8	
PND 4 (post culling)	M	10.5	10.8	11.5**	11.1	
	F	10.2	10.4	11.2*	10.6	
	M + F	10.3	10.6	11.4**	10.8	
PND 7	M	16.6	16.8	17.8*	16.8	14.7 – 17.6
	F	16.1	16.2	17.2*	16.2	14.2 – 16.9
	M + F	16.4	16.5	17.5*	16.5	14.7 – 17.3
PND 14	M	33.0	32.8	34.3	32.6	29.3 – 35.1
	F	32.2	32.0	33.3	31.7	28.7 – 34.2
	M + F	32.6	32.4	33.8	32.1	29.2 – 34.7
PND 21	M	51.8	51.4	53.4	50.8	46.5 – 58.3
	F	50.3	49.6	51.5	49.0	45.5 – 55.7
	M + F	51.1	50.5	52.4	49.8	46.2 – 56.8

- *External, soft tissue and skeletal malformations and other relevant alterations:*
    - *Tot. nb of pup with necropsy observations:* 10, 15, 14 and 8 pups, resp. at 0, 20, 100 and 300 mg (no treatment related effects observed).

3.10.1.3 Prenatal toxicity study in Wistar rats (Anonymous, 1997)

Study reference

Anonymous, 1997

Detailed study summary and results

Test type

OECD TG 414

GLP

Test substance

- DMPP
- *Degree of purity:* 97.1 %

Test animals

- *Species/strain/sex:* Rat / Wistar / female
- *Nb. of animals per sex per dose:* 25 mated females/dose (23-25 pregnant females/dose)
- *Age and weight at the study initiation:* approx. 12 weeks and 244 g at GD 0.

Administration/exposure

- *Route of administration:* oral, gavage
- *Duration and frequency of test/exposure period:* GD 6 to 15, daily
- *Doses/concentration levels, rationale for dose level selection:* 0, 25, 100 and 400 mg/kg bw/d
- *Vehicle:* /

Results and discussion

For P adults (per dose):

- *Nb. of animals at the start of the test and mating:* 25 females per group were mated.

  0, 1, 1 and 2 females were not pregnant, resp. at 0, 25, 100 and 400 mg/kg bw/d.
- *Time of death during the study and whether animals survived to termination:* no mortality occurred during the study period.
- *Clinical observations:* at the highest dose, 12 females out of 25 exhibited transient excessive salivation immediately after exposure.
- *Food consumption:*

Table 61: Mean food consumption (in g/animal/day)

Dose level (in mg/kg bw/d)	0	25	100	400
Nb of animals	3	4	2	9
D 0 to 6	21.4	21.5	21.9	21.4
D 6 to 15	24.6	24.9	25.0	23.8
D 15 to 20	27.3	27.6	27.7	28.1
D 0 to 20	24.2	24.4	24.6	23.9

- *Body weight data:*

Table 62: Body weight data (in g)

Dose level (in mg/kg bw/d)	0	25	100	400	HCD range of actual values (01/94 to 10/96)
Nb of animals	25	24	24	23	
D 0	242.2	244.8	244.5	244.0	211.5 – 293.3
D 6	269.4	272.3	274.0	271.0	224.8 – 317.9
D 10	286.3	289.2	289.4	282.5	241.6 – 337.3
D 15	314.8	318.3	317.8	316.1	265.1 – 368.7
D 20	384.3	388.7	386.1	384.2	309.9 – 460.5

- *Toxic response data by sex and dose including indices of mating, fertility, gestation, birth, viability and lactation; indicate the numbers used in calculating the indices:*

Table 63: Reproduction data

Dose level (in mg/kg bw/d)	0	25	100	400
Nb of females mated	25	25	25	25
Nb of pregnant females	25	24	24	23
Nb of dams with viable fetuses	25	24	24	23

No females with abortion or premature births.

- *Haematological and clinical biochemistry findings:* not examined
- *Effects on sperm:* /
- *Nb. of females cycling normally and cycle length:* /
- *Duration of gestation (calculated from day 0 of pregnancy):* /
- *Precoital interval (number of days until mating and number of estrous periods until mating):* /

- *Nb. of implantations, corpora lutea, litter size:*
    - *Mean nb of corpora lutea:* 15.4, 15.6, 15.9 and 15.3, resp. at 0, 25, 100 and 400 mg/kg bw/d (HCD range (01/94 to 10/96): 14.9 to 16.5).
    - *Mean nb of implantation sites:* 14.4, 14.6, 13.9 and 14.2, resp. at 0, 25, 100 and 400 mg/kg bw/d (HCD range (01/94 to 10/96): 13.4 to 15.8).
- *Mean % of pre- and post-implantation loss:*
    - *Pre-:* 7.1, 6.6, 14.4 and 7.8 %, resp. at 0, 25, 100 and 400 mg/kg bw/d (HCD range (01/94 to 10/96): 2.9 to 13.6).
    - *Post-:* 11.5, 6.3, 9.0 and 11.3 %, resp. at 0, 25, 100 and 400 mg/kg bw/d (HCD range (01/94 to 10/96): 4.4 to 10.8).
- *Nb. of dams with abortions, early deliveries, stillbirths, resorptions and/or dead fetuses:*
    - *Mean tot resorption:* 1.6, 1.0, 1.2 and 1.5, resp. at 0, 25, 100 and 400 mg/kg bw/d (HCD range (01/94 to 10/96): 0.7 to 1.6).
    - *Mean early resorption:* 1.6, 0.9, 1.1 and 1.4, resp. at 0, 25, 100 and 400 mg/kg bw/d.
    - *Mean late resorption:* 0.0, 0.0, 0.1 and 0.1, resp. at 0, 25, 100 and 400 mg/kg bw/d.
    - *Dead fetuses:* 0 in all groups.
- *Nb. of live births:*

Table 64: Live fetuses

Dose level (in mg/kg bw/d)	0	25	100	400
Mean nb of live fetuses	12.8	13.7	12.7	12.7
Mean nb of live females	6.1	6.8	6.9	6.7
Mean nb of live males	6.7	6.9	5.8	6.0

- *Necropsy findings:* no treatment-related abnormalities observed (24, 25, 24 and 24 females without findings, resp. at 0, 25, 100 and 400 mg/kg bw/d).
- *Organ weight:* NE
- *Histopathological findings:* NE
- *Body weight change and gravid uterine weight, including optionally, body weight change corrected for gravid uterine weight:*

Table 65: Mean gravid uterus weight and net maternal body weight change

Dose level (in mg/kg bw/d)	0	25	100	400
Nb of animals	25	24	24	23
Gravid uterus weight (g)	75.4	81.3	74.2	71.9
Carcass weight (g)	308.9	307.4	312.0	312.3
Net weight change from GD 6	39.5	35.2	38.0	41.3

For F1 pups/litters (per dose):

- *Mean number of live pups (litter size):*

Table 66: Mean nb of live pups

Dose level (in mg/kg bw/d)	0	25	100	400
Mean nb of live fetuses	12.8	13.7	12.7	12.7
Mean nb of live females	6.1	6.8	6.9	6.7
Mean nb of live males	6.7	6.9	5.8	6.0

Litter size: HCD range (01/94 to 10/96): 12.4 to 14.8.

- *Sex ratio:* 47.5, 49.4, 54.4 and 52.5 % of females, resp. at 0, 25, 100 and 400 mg/kg bw/d.
- *Viability index (pups surviving 4 days/total births):* /
- *Survival index at weaning:* /
- *Mean litter or pup weight by sex and with sexes combined:*

Table 67: Mean fetal and placental weight (in g)

Dose level (in mg/kg bw/d)		0	25	100	400	HCD range (01/94 to 10/96)
Mean placental weight	All viable fetuses	0.45	0.44	0.44	0.42	0.32 – 0.60
	M fetuses	0.44	0.44	0.43	0.42	0.33 – 0.61
	F fetuses	0.45	0.43	0.44	0.42	0.31 – 0.62
Mean fetal weight	All viable fetuses	3.91	3.93	3.89	3.78	3.2 – 4.6
	M fetuses	4.01	4.03	3.98	3.85	2.9 – 4.2
	F fetuses	3.83	3.81	3.80	3.71	3.2 – 4.4

- *External, soft tissue and skeletal malformations and other relevant alterations:*
  - *External malformation:* one animal of the mid dose exhibited anophthalmia and shortened tail.

Table 68: Incidence of external malformation/variation

Dose level (in mg/kg bw/d)		0	25	100	400
Nb of litters evaluated		25	24	24	23
Nb of fetuses evaluated		320	328	305	291
Total malformations	Fetal inc	0	0	1	0
	Litter inc	0	0	1	0
Total variations	Fetal inc	0	0	0	0
	Litter inc	0	0	0	0

  - *Soft tissue observations:* at the mid dose, hydrocephaly and dilatation of both ventricules (globular shaped heart) were observed in one fetus of the mid dose group.
  - *Skeletal observations:* fetal incidence of malformations: 1, 3, 0 and 5 fetuses, resp. at 0, 25, 100 and 400 mg/kg bw/d (mean % of affected fetuses/liter: 0.6, 1.9, 0.0 and 4.5* %, resp. at 0, 25, 100 and 400 mg/kg bw/d).

Table 69: Fetal incidence of skeletal malformations

Dose level (in mg/kg bw/d)	0	25	100	400
Nb of litters evaluated	25	24	24	23
Nb of fetuses evaluated	167	169	156	150

Vertebrae fused and/or of irregular shape	0	0	0	1
Thoracic vertebra absent	0	1	0	0
Lumbar vertebra absent	0	0	0	1
Scapula shortened	1	0	0	0
Sternebra bipartite, ossification centers dislocated	1	2	0	3
Bifurcated rib(s)	0	0	0	1
Humerus shortened and bent	1	0	0	0

3.10.1.4 Prenatal developmental toxicity screening study in Himalayan rabbits (Anonymous, 2007)

Study reference

Anonymous, 2007

Detailed study summary and results

Test type

GLP

Test substance

- DMPP
- *Degree of purity:* 97 %

Test animals

- *Species/strain/sex:* Rabbit / Himalayan / female
- *Nb. of animals per sex per dose:* 5 inseminated females/group
- *Age and weight at the study initiation:* no information available

Administration/exposure

- *Route of administration:* oral, gavage
- *Duration and frequency of test/exposure period:* GD 6 to 28, daily
- *Doses/concentration levels, rationale for dose level selection:* 0, 25, 100 and 400 mg/kg bw/d
- *Historical control data:* not available
- *Vehicle:* no information available

Results and discussion

For P adults (per dose):

- *Time of death during the study and whether animals survived to termination:* at the highest dose: all females were sacrificed in a moribund state at GD 14-15 (2 at GD 14 and 3 at GD 15).
- *Clinical observations:* at the highest dose, severe clinical signs were observed such as lateral position (4 females out of 5), apathy and poor general state (all females), hypothermia (3 out of 5). These clinical signs were observed at GD 14. No defecation on day 8-15 (all animals).

  Mid dose: reduced defecation on GD 8-11 in all females.

  Control and low dose: no effects.

- *Food consumption:*

Table 70: Mean food consumption (in g/animal/day)

Dose level (in mg/kg bw/d)	0	25	100	400
GD 0 to 6	92.9	97.0	92.6	102.1
GD 6 to 28	72.9	78.7	70.0	70.6
GD 0 to 29	77.0	82.7	75.1	41.2

- *Body weight data:*

Table 71: Body weight (in g)

Dose level (in mg/kg bw/d)	0	25	100	400
GD 0	2491	2564	2547	2583
GD 6	2539	2591	2571	2630
GD 9	2526	2595	2536	2458
GD 14	2562	2641	2579	2302*
GD 21	2590	2680	2617	-
GD 29	2727	2849	2746	-

- *Toxic response data by sex and dose including indices of mating, fertility, gestation, birth, viability and lactation:*

Table 72: Reproduction data

Dose level (in mg/kg bw/d)	0	25	100	400
Nb of females mated	5	5	5	5
Nb of pregnant females	4	5	5	5
Nb of dams with viable fetuses	4	5	5	0

- *Haematological and clinical biochemistry findings:* not examined
- *Effects on sperm:* /
- *Nb. of females cycling normally and cycle length:* /
- *Duration of gestation (calculated from day 0 of pregnancy):* /
- *Precoital interval (number of days until mating and number of estrous periods until mating):* /
- *Nb. of implantations, corpora lutea, litter size:*
    - *Mean nb of corpora lutea:* 8.0, 8.4 and 7.4, resp. at 0, 25 and 100 mg/kg bw/d.
    - *Mean nb of implantation sites:* 7.8, 8.2 and 5.6, resp. at 0, 25 and 100 mg/kg bw/d.
- *Mean % of pre- and post-implantation loss:*
    - *Pre-:* 3.1, 2.9 and 23.8** %, resp. at 0, 25 and 100 mg/kg bw/d.
    - *Post-:* 3.1, 2.9 and 9.7 %, resp. at 0, 25 and 100 mg/kg bw/d.
- *Nb. of dams with abortions, early deliveries, stillbirths, resorptions and/or dead fetuses:*

Table 73: Resorption

Dose level (in mg/kg bw/d)	0	25	100
Mean tot resorption	0.3	0.2	0.6

Mean early resorption	0.3	0.2	0.4
Mean late resorption	0.0	0.0	0.2
Nb of dead fetuses	0	0	0

- *Nb. of live births:*

Table 74: Mean nb of live fetuses

Dose level (in mg/kg bw/d)	0	25	100	400
Mean nb of live fetuses	7.5	8.0	5.0	0
Mean nb of female live fetuses	3.5	3.4	3.0	0
Mean nb of male live fetuses	4.0	4.6	2.0**	0

- *Necropsy findings:* 1 female of the mid dose group had absent lung lobe (lobe inferior medialis).

  At the highest dose, all animals had hairball in stomach, no feces in intestines.
- *Body weight at sacrifice and absolute and relative organ weight data for the parental animals:* not examined.
- *Histopathological findings:* not examined.
- *Body weight change and gravid uterine weight, including optionally, body weight change corrected for gravid uterine weight:*

Table 75: Mean gravid uterus weight and net maternal body weight change (in g)

Dose level (in mg/kg bw/d)	0	25	100	400
Nb animals examined	4	5	5	0
Gravid uterus weight	379.8	392.8	269.5*	/
Carcass weight	2347.4	2455.8	2476.3	/
Net weight change from GD 6	-191.8	-134.8	-94.3	/

For F1 pups/litters (per dose):

- *Mean number of live pups (litter size):*

Table 76: Live fetus data

Dose level (in mg/kg bw/d)	0	25	100	400
Mean nb of live fetuses	7.5	8.0	5.0	0
Mean nb of female live fetuses	3.5	3.4	3.0	0
Mean nb of male live fetuses	4.0	4.6	2.0**	0

- *Sex ratio:* 46.7, 42.5 and 60.0 % of females, resp. at 0, 25 and 100 mg/kg bw/d.
- *Viability index (pups surviving 4 days/total births):* /
- *Survival index at weaning:* /
- *Mean litter or pup weight by sex and with sexes combined:*

Table 77: Mean placental and fetal bw (in g)

Dose level (in mg/kg bw/d)		0	25	100
Placental weight	All viable fetuses	4.6	4.7	4.8

	M fetuses	4.7	4.6	5.0
	F fetuses	4.5	4.4	4.7
Fetal weight	All viable fetuses	37.5	36.7	38.6
	M fetuses	37.8	35.8	40.5
	F fetuses	36.9	37.0	37.9

- *External, soft tissue and skeletal malformations and other relevant alterations:*
  - *External observation:* 2 fetuses of the low dose group exhibited variations (paw hyperflexion).
  - *Soft tissue observation:* 1, 2 and 0 fetuses exhibited malformation, resp. at 0, 25 and 100 mg/kg bw/d (absent subclavian or absent gallbladder).
  - *Skeletal observation:* only 1 fetuse of the low dose group exhibited skeletal malformation (misshapen cervical vertebra).

3.10.1.5 Prenatal toxicity study in Wistar rat (Anonymous, 1996)

Study reference

Anonymous, 1996

Detailed study summary and results

Test type

Similar to OECD TG 414

Test substance

- 3,4-dimethylpyrazole-phosphat
- *Degree of purity:* information not available

Test animals

- *Species/strain/sex: R*at / Wistar / female
- *Nb. of animals per sex per dose:* 10/group
- *Age and weight at the study initiation:* approx. 240 g

Administration/exposure

- *Route of administration:* oral, gavage
- *Duration and frequency of test/exposure period:* GD 6 to 15, daily
- *Doses/concentration levels, rationale for dose level selection:* 0, 20, 80 and 320 mg/kg bw/d
- *Historical control data:* not available
- *Vehicle:* 0.5 % CMC

Results and discussion

For P adults (per dose):

- *Time of death during the study and whether animals survived to termination:* no mortality occurred during the study period.

- *Clinical observations:* no treatment-related effects.
- *Food consumption:* no treatment-related effect.

Table 78: Food consumption (in g/animal/day)

Dose level (in mg/kg bw/d)	0	20	80	320
GD 0 to 6	21.3	21.4	22.0	21.7
GD 6 to 15	24.8	25.2	25.3	23.5
GD 15 to 50	27.0	28.1	28.3	28.3
GD 0 to 20	24.1	24.5	24.8	24.0

- *Body weight data:* no treatment-related effect.

Table 79: Body weight and body weight gain (in g)

Dose level (in mg/kg bw/d)	0	20	80	320
GD 0	242.5	241.9	242.4	241.4
GD 6	267.0	268.1	267.2	265.6
GD 10	286.0	284.9	282.8	274.0
GD 15	312.3	312.0	311.0	303.4
GD 20	380.0	380.2	380.9	377.7
BWG GD 6 to 15	45.4	43.9	43.7	37.8
BWG GD 0 to 20	137.5	138.3	138.5	136.3

- *Haematological and clinical biochemistry findings:* not examined
- *Effects on sperm:* /
- *Nb. of females cycling normally and cycle length:* /
- *Duration of gestation (calculated from day 0 of pregnancy):* /
- *Precoital interval (number of days until mating and number of estrous periods until mating):* /
- *Nb. of implantations, corpora lutea, litter size:*
    - *Mean nb of corpora lutea:* 16.2, 15.7, 16.5 and 16.6, resp. at 0, 20, 80 and 320 mg/kg bw/d.
    - *Mean nb of implantation sites:* 15.0, 13.0, 15.1 and 15.1, resp. at 0, 20, 80 and 320 mg/kg bw/d.
- *Mean % of pre- and post-implantation loss:*
    - *Pre-:* 8.0, 18.3, 8.7 and 8.8 %, resp. at 0, 20, 80 and 320 mg/kg bw/d.
    - *Post-:* 8.4, 2.5, 4.8 and 4.1 %, resp. at 0, 20, 80 and 320 mg/kg bw/d.
- *Mean number of resorptions:*
    - *Total:* 1.3, 0.4, 0.7 and 0.6, resp. at 0, 20, 80 and 320 mg/kg bw/d.
    - *Early:* 1.0, 0.3, 0.5 and 0.4, resp. at 0, 20, 80 and 320 mg/kg bw/d.
    - *Late:* 0.3, 0.1, 0.2 and 0.2, resp. at 0, 20, 80 and 320 mg/kg bw/d.
- *Number of dams with abortions, early deliveries, stillbirths and/or dead fetuses:*

Table 80: Reproduction data

Dose level (in mg/kg bw/d)	0	20	80	320

Nb of pregnant females	9	10	10	10
Nb of aborted	0	0	0	0
Nb of dams with viable fetuses	9	10	10	10
Nb of dams with all resorptions	0	0	0	0

- *Mean number of live births:* 13.7, 12.6, 14.4 and 14.5, resp. at 0, 20, 80 and 320 mg/kg bw/d.
- *Necropsy findings:* nothing abnormal detected in 7, 9, 9 and 7 females, resp. at 0, 20, 80 and 320 mg/kg bw/d. In other animals, marginal emphysema and edema in lungs were observed (also in control group).
- *Organ weight:*

Table 81: Organ weight (in g or %)

Dose level (in mg/kg bw/d)		0	20	80	320
FBW		380.0	380.2	380.9	377.7
Kidneys	Abs	1.91	2.03	1.96	1.96
	Rela	0.502	0.537	0.514	0.519
Liver	Abs	16.11	17.25	16.89	15.96
	Rela	4.238	4.553	4.439	4.226

- *Histopathological findings:* not examined
- *Body weight change and gravid uterine weight, including optionally, body weight change corrected for gravid uterine weight:*

Table 82: Gravid uterus weight (in g)

Dose level (in mg/kg bw/d)	0	20	80	320
Gravid uterus weight (in g)	78.2	71.5	80.4	81.6
Carcass weight (in g)	301.9	308.7	300.5	296.1
Net weight change from GD 6	34.9	40.6	33.3	30.5

For F1 pups/litters (per dose):

- *Mean number of live pups (litter size):*

Table 83: Litter size

Dose level (in mg/kg bw/d)	0	20	80	320
Mean nb of live fetuses	13.7	12.6	14.4	14.5
Mean nb of females	7.2	6.1	7.0	7.5
Mean nb of males	6.4	6.5	7.4	7.0

- *Sex ratio:* 52.8, 48.4, 48.6 and 51.7 % of live females, resp. at 0, 20, 80 and 320 mg/kg bw/d.
- *Viability index (pups surviving 4 days/total births):* /
- *Survival index at weaning:* /
- *Placental and fetal weight:*

Table 84: Mean placental and fetal weight (in g)

Dose level (in mg/kg bw/d)		0	20	80	320
Placental weight	All viable fetuses	0.48	0.50	0.45	0.44
	Male fetuses	0.49	0.50	0.46	0.45
	Female fetuses	0.46	0.49	0.45	0.44
Fetal weight	All viable fetuses	3.8	3.8	3.8	3.8
	Male fetuses	3.9	3.8	3.9	3.9
	Female fetuses	3.7	3.7	3.7	3.7

- *Mean litter or pup weight by sex and with sexes combined:* /
- *External, soft tissue and skeletal malformations and other relevant alterations:*
  - *External observations:* no malformations or variations observed.
  - *Soft tissue observations:* no malformations observed. Soft tissue variations was observed in 7, 10, 12 and 13 fetuses, resp. at 0, 20, 80 and 320 mg/kg bw/d (such as dilated renal pelvis in 7, 10, 12 and 13 fetuses and hydroureter in 0, 2, 2 and 1 fetuses, resp. at 0, 20, 80 and 320 mg/kg bw/d).
  - *Skeletal observations:* malformations were observed in 3, 5, 1 and 4 fetuses, resp. at 0, 20, 80 and 320 mg/kg bw/d.

Table 85: Fetal incidence of skeletal malformations

Dose level (in mg/kg bw/d)	0	20	80	320
Thoracic vertebral body/bodies dumbbell-shaped	3	3	1	4
Thoracic vertebral body/bodies bipartite	0	2	0	0
Sternebra bipartite, ossification centers dislocated	0	1	0	0

Variations were observed in 27, 29, 28 and 50 fetuses, resp. at 0, 20, 80 and 320 mg/kg bw/d.

Table 86: Fetal incidence of skeletal variations

Dose level (in mg/kg bw/d)	0	20	80	320
Sternebra of irregular shape	15	13	14	23
Sternebra bipartite	1	4	2	7
13^{th} rib(s) shortened	14	11	11	28
Rudimentary cervical rib(s)	0	0	2	2
Accessory 14^{th} rib(s)	0	0	2	0

3.10.1.6 Toxicity study concerning the influence of DMPP on the phosphate metabolism of adult rats and suckling pups (Anonymous, 2017)

Study reference

Anonymous, 2017

Detailed study summary and results

Test type

Aim of the study: "obtain general information on the possible effects of DMPP on the integrity and performance of the female phosphate metabolism" as well as "preliminary data on postnatal developmental toxicity".

Test substance

- DMPP
- *Degree of purity:* 99.4 g/100 g

Test animals

- *Species/strain/sex: R*at / Wistar / female
- *Nb. of animals per sex per dose:* 15 female rats/group
- *Age and weight at the study initiation:* approx. 35 days

Administration/exposure

- *Route of administration:* oral, diet
- *Duration and frequency of test/exposure period:* 10 weeks of premating period, maximum 14 days of mating period, during gestation and lactation periods until sacrifice.
- *Doses/concentration levels, rationale for dose level selection:* 0 or 500 mg/kg bw/d
- *Positive control group:* calcitriol 0.00045 mg/kg bw/d (given by gavage) (1alpha,25-dihydroxyvitamin D3)
- *Historical control data:* information not available
- *Vehicle:* /

Description of test design:

- *Details on mating procedure (M/F ratios per cage, length of cohabitation, proof of pregnancy):* all females were paired with untreated males.

Results and discussion

- *Mean substance intake:*

During premating and mating period (W 0 – 10): 493.8 mg/kg bw/d

Gestation period (GD 0 – 20): 450.5 mg/kg bw/d

Lactation period (LD 0 – 20): 423.6 mg/kg bw/d

For P adults (per dose):

- *Nb. of animals at the start of the test and mating:* 10/group
- *Time of death during the study and whether animals survived to termination:* no treatment-related mortality.
- *Clinical observations:* no treatment-related effects during premating and mating period.

During gestation period, one female had blood in bedding.

During lactation period, 3 complete litter loss and 1 other not properly nursed.

- *Food consumption:* premating and mating period: mean (day 0-69): 12.3 and 13.8* g/animal/d, resp. at 0 and 500 mg/kg bw/d and 12.1 g/animal/d in positive control group.

  Gestation period: mean (GD 0 – 20): 19.4 and 14.5** g/animal/day, resp. at 0 and 500 mg/kg bw/d and 14.2** g/animal/d in positive control group.

- *Body weight data:*

Table 87: Body weight (in g)

Dose level (in mg/kg bw/d)		0	500	PC
Premating and mating period	D 0	106.5	106.2	106.2
	D 69	213.0	209.2	221.4
	BWG D 0 to 69	106.5	103.0	115.2
Gestation period	GD 0	217.5	216.7	221.2
	GD 7	237.3	223.3	233.2
	GD 14	263.1	238.2**	248.0
	GD 20	315.1	280.6**	296.8
	BWG GD 0 to 20	97.6	63.9**	75.5*
Lactation period	LD 1	243.2	228.8	236.6
	LD 4	260.3	231.8**	246.4
	LD 7	265.1	235.0**	256.4
	LD 14	275.2	250.7**	273.9
	BWG LD 1 to 14	32.0	21.8	37.3

- *Haematological and clinical biochemistry findings:*

Table 88: Blood parameters (at PND 15)

Dose level (in mg/kg bw/d)	0	500	PC
Nb animals examined	14	9	13
INP (mmol/L)	2.46	2.21	2.65
Ca (mmol/L)	2.59	2.62	2.94**
PTH (pg/mL)	469.20	451.58	33.12**
1.25 vit D (pmol/L)	66	177**	91
Calcitonin (ng/L)	143.03	371.32	232.77

- *Parameters in rat milk:*

Table 89: Parameters in rat milk (at PND 12)

Dose level (in mg/kg bw/d)	0	500	PC
Tot. prot. (g/L)	4.97	5.28	5.03
Trig (mmol/L)	5.14	5.68	5.35
Lactose (g/L)	36.24	30.71**	36.62

- *Effects on sperm:* /
- *Nb. of P females cycling normally and cycle length:* /
- *Mating data:*

Table 90: Mating data and fertility index

Dose level (in mg/kg bw/d)	0	500	PC
Nb of females mated	15	15	15
Nb of pregnant females	14	13	14
Female fertility index (in %)	93.3	86.7	93.3

- *Precoital interval (number of days until mating and number of estrous periods until mating):*
  - *Mating days until GD 0:* 3.3 and 3.5 days, resp. at 0 and 500 mg/kg bw/d (3.9 days in positive control group).
- *Nb. of implantations, corpora lutea, litter size:*
  - *Mean nb of implantation sites:* 11 and 9, resp. at 0 and 500 mg/kg bw/d (12 in positive control group).
- *Nb. of pre- and post-implantation loss:*
  - *% of post-implantation loss:* 12 and 20 %, resp. at 0 and 500 mg/kg bw/d (17 in positive control group).
- *Duration of gestation (calculated from day 0 of pregnancy):* 22.3 and 22.8* days, resp. at 0 and 500 mg/kg bw/d (22.2 days in positive control).
- *Nb. of dams with abortions, early deliveries, stillbirths, resorptions and/or dead fetuses:*

Table 91: Pregnancy report

Dose level (in mg/kg bw/d)		0	500	PC
Nb of pregnant females		14	13	14
Nb of pregnant female without delivery		0	1	1
Nb of delivery	Mean nb of pups (liveborn and stillborn)	14	12	13
	With liveborn pups (gestation index in %)	14 (100)	10 (76.5)	13 (92.9)
	With all stillborn pups	0	2	0

  - *Nb. of females with stillborn pups:* 1 and 6* females, resp. at 0 and 500 mg/kg bw/d (2 females in positive control).
- *Nb. of live births:* live birth index: 99.3 and 76.0 %, resp. at 0 and 500 mg/kg bw/d (98.6 % in positive control).
- *Data on functional observations:* /
- *Necropsy findings:* no treatment-related findings.
- *Organ weight:* NE
- *Histopathological findings:* NE
- *Body weight change and gravid uterine weight, including optionally, body weight change corrected for gravid uterine weight:* NE

For F1 pups/litters (per dose):

- *Mean nb of live pups (litter size):*

Table 92: Litter data

Dose level (in mg/kg bw/d)	0	500	PC
Total nb of pups delivered	139	96	142
Mean nb of pups delivered	10	8	11
Tot nb of pups stillborn	1	23	2
Tot nb of pups liveborn	138	73	140
Mean nb of liveborn pups	10	6**	11
Nb of pups found dead/dead	0	8	2
Nb of pups cannibilized	0	4	3
Nb sacrificed scheduled	138	61	135

Table 93: Mean nb of live pups/litter

Dose level (in mg/kg bw/d)	0	500	PC
D 0	10	7* (St. Dev. 2)	11
D 4	10	6** (St. Dev. 3)	10
D 7	10	7** (St. Dev. 1)	10
D 14	10	7** (St. Dev. 1)	10

- *Sex ratio:*
  - *At D 0:* 55/45 and 36/64 % of live male/live female pups, resp. at 0 and 500 mg/kg bw/d (47/53 % of live male/live female pups in positive control group).
  - *At D 14:* 55/45 and 35/65 % of live male/live female pups, resp. at 0 and 500 mg/kg bw/d (47/53 % of live male/live female pups in positive control group).
- *Viability index (pups surviving 4 days/total births):* /
- *Survival index at weaning:* /
- *Nb. of litters not surviving at day 14:* 0 and 3, resp. at 0 and 500 mg/kg bw/d (0 in positive control group).

Table 94: Pups mortality

Dose level (in mg/kg bw/d)	0	500	PC
Nb of pups delivered	139	96	142
At D 0	0	3	0
D 1 to 4	0	9	5
D 5 to 7	0	0	0
D 8 to 14	0	0	0
Nb of pups surviving D 0 to 14	138	61	135
Survival index (at D 14)	100	87	96

- *Mean litter or pup weight by sex and with sexes combined:*

Table 95: Pups body weight (in g)

Dose level (in mg/kg bw/d)		0	500	PC
PND 1	M + F	7.0	5.7**	6.6

	M	7.2	6.2**	6.7
	F	6.8	5.5**	6.4
PND 4	M + F	11.0	9.4**	10.2
	M	11.3	9.7*	10.4
	F	10.7	9.1*	10.0
PND 7	M + F	16.2	13.8*	15.0
	M	16.6	14.1	15.1
	F	15.8	13.5*	14.8
PND 14	M + F	29.6	26.2	27.7
	M	30.0	26.9	28.0
	F	28.7	25.7	27.3
BWG D 1 - 14	M + F	22.6	20.2	21.1

- *Pups necropsy:*
    - *Males:* 1 male of the control group had testis malpositionned and renal pelvis dilated. No findings was observed in another groups.
    - *Females:* 2 female pups of the high group had stomach empty and 1 female pups of the positive control group had abdomen fluid-filled.
- *External, soft tissue and skeletal malformations and other relevant alterations:* /
- *Nb. and percent of fetuses and litters with malformations (including runts) and/or variations as well as description and incidences of malformations and main variations (and/or retardations):* /
- *Data on physical landmarks in pups and other postnatal developmental data:* /
- *Data on functional observations:* /

3.10.2 Human data

No human data available

3.10.3 Other data (e.g. studies on mechanism of action)

No other data available

3.11 Specific target organ toxicity – single exposure

Hazard class not assessed in this dossier

3.12 Specific target organ toxicity – repeated exposure

3.12.1 Animal data

3.12.1.1 Test/Palatability study in Wistar rats (Anonymous, 2002)

Study reference

Anonymous, 2002

Detailed study summary and results

Test type

Range-finding: to select doses for the subchronic toxicity study

Test substance

- DMPP
- *Degree of purity:* no information available

Test animals

- *Species/strain/sex:* Rat / Wistar / both sexes
- *Nb. of animals per sex per dose:* 3/sex/dose
- *Age and weight at the study initiation:* no information available

Administration/exposure

- *Route of administration:* oral, in diet
- *Duration and frequency of test/exposure period:* 2 weeks
- *Doses/concentration levels, rationale for dose level selection:* 0, 5000 and 10000 ppm
- *Post exposure observation period:* /
- *Vehicle:* no information available
- *Actual dose (mg/kg bw/day) and conversion factor from diet/drinking water test substance concentration (ppm) to the actual dose, if applicable:* no information available

Results and discussion

- *Mortality and time to death (if occurring):* no mortality occurred during the study period.
- *Description, severity, time of onset and duration of clinical signs (reversible, irreversible, immediate, delayed):* no effects observed.
- *Body weight and body weight changes:* sign changes observed in males at the highest dose.

Table 96: Mean body weight data (in g)

	Males			Females		
Dose level (in ppm)	0	5000	10000	0	5000	10000
D 0	150.0	154.5 (+3.0 %)	146.2 (-2.5 %)	119.0	117.4 (-1.3 %)	111.7 (-6.1 %)
D 7	190.2	189.9 (-0.1 %)	162.9* (-14.4 %)	137.5	132.0 (-4.0 %)	121.7 (-11.5 %)
D 14	228.4	233.6 (+2.3 %)	191.1* (-16.3 %)	151.5	145.2 (-4.1 %)	135.1 (-10.8 %)
BWG D 0 - 14	78.4	79.2 (+1.0 %)	44.8* (-42.8 %)	32.5	27.8 (-14.4 %)	23.4 (-27.9 %)

- *Food/water consumption:*

Table 97: Mean food consumption (in g/animal/day)

	Males			Females		
Dose level (in ppm)	0	5000	10000	0	5000	10000
D 7	19.4	18.8 (-3.4 %)	13.1** (-32.6 %)	14.0	12.0 (-14.7 %)	10.0** (-28.9 %)
D 14	21.9	22.0 (+0.7 %)	17.3 (-20.9 %)	15.3	14.5 (-5.3 %)	13.1 (-14.9 %)

Table 98: Mean water consumption (in g/animal/day)

	Males			Females		
Dose level (in ppm)	0	5000	10000	0	5000	10000
D 7	18.9	29.2** (+54.7 %)	21.1 (+11.5 %)	13.2	17.8 (+34.7 %)	13.0 (-1.9 %)
D 14	24.0	24.8 (+3.5 %)	20.5 (-14.2 %)	15.6	19.9 (+27.6 %)	18.1 (+16.2 %)

- *Sensory activity, grip strength and motor activity assessments (when available):* NE
- *Ophthalmologic findings:* NE
- *Haematological findings:* NE
- *Clinical biochemistry findings:* NE
- *Gross pathology findings:* no information available
- *Histopathology findings:* NE

3.12.1.2 Repeated dose 28-day oral toxicity study in Wistar rats (Anonymous, 2021)

Study reference

Anonymous, 2021

Detailed study summary and results

Test type

OECD TG 407

GLP

Test substance

- DMPP
- *Degree of purity:* 99.4 %

Test animals

- *Species/strain/sex:* Rat / Wistar / both sexes
- *Nb. of animals per sex per dose:* 5/sex/dose
- *Age and weight at the study initiation:* 42 ± 1 D

Administration/exposure

- *Route of administration:* oral, in diet
- *Duration and frequency of test/exposure period:* 4 weeks, daily
- *Doses/concentration levels, rationale for dose level selection:* 0, 1500, 3000 and 6500 ppm
- *Post exposure observation period:* /
- *Vehicle:* Ground kliba maintenance diet mouse/rat GLP meal
- *Actual dose (mg/kg bw/day) and conversion factor from diet/drinking water test substance concentration (ppm) to the actual dose, if applicable:*

Table 99: Mean daily test-substance intake

	Males				Females			
Dose level (in ppm)	0	1500	3000	6500	0	1500	3000	6500
Mean daily test substance intake (in mg/kg bw/d)	0	126.8	215.7	510.4	0	130.7	255.4	488.7

Results and discussion

- *Mortality and time to death (if occurring):* no mortality occurred during the study period.
- *Description, severity, time of onset and duration of clinical signs (reversible, irreversible, immediate, delayed):* no treatment-related effects.
- *Body weight and body weight changes:*

Table 100: Mean body weight data (in g)

	Males				Females			
Dose level (in ppm)	0	1500	3000	6500	0	1500	3000	6500
D 0	160.0	162.0	156.9	161.5	128.9	127.9	127.7	128.1
D 7	204.0	206.9	193.1	198.2	151.0	152.5	151.2	147.2
D 11	-	-	-	-	161.6	159.6	159.2	159.4
D 14	247.5	249.3	234.0	244.0	169.2	169.0	168.0	168.8
D 21	277.3	278.3	261.6	276.0	180.5	180.4	183.8	181.8
D 28	294.0	295.5	278.3	295.0	193.3	189.3	197.7	190.8
BWG D 0 to 28	134.0	133.5	121.4	133.5	64.4	61.4	70.0	62.7

- *Food/water consumption:*

Table 101: Mean food consumption (in g/animal/day)

	Males				Females			
Dose level (in ppm)	0	1500	3000	6500	0	1500	3000	6500
D 6 to 7	18.4	23.7	15.4	12.7	12.7	13.6	13.2	13.0
D 10 to 11	/	/	/	/	11.2	13.2	13.2	14.5
D 13 to 14	20.3	19.6	17.4	25.9	24.6	16.1	14.2	12.4
D 20 to 21	21.3	20.4	18.6	20.0	17.2	13.7	14.9	12.2
D 27 to 28	19.3	21.1	17.4	21.0	15.9	16.7	17.2	13.7

- *Sensory activity, grip strength and motor activity assessments (when available):* no treatment-related effects.
    - *FOB:*

Table 102: FOB data

	Males				Females			
Dose level (in ppm)	0	1500	3000	6500	0	1500	3000	6500
Mean Rearing (D 24/26 in M/F) (N)	2	2	5	3	13	13	16	11
Mean GS F (D 24/26 in M/F) (Newton)	9.7	10.3	9.5	9.9	8.4	9.1	9.8	8.4
Mean GS H (D 24/26 in M/F) (Newton)	7.2	7.0	7.3	6.3	4.8	4.3	4.1	4.0
Mean FST (D 24/26 in M/F) (cm)	10.5	10.0	9.7	9.7	10.0	10.1	10.3	8.8

- *Home cage observation:* no tremors, convulsions, abnormal movements observed.
- *Open field observation:* no effects observed.
- *Sensorimotor tests/reflexes:* no effects observed.
- *Motor activity:*

Table 103: Sum beam interrupts

	Males				Females			
Dose level (in ppm)	0	1500	3000	6500	0	1500	3000	6500
Interv. 1-12: Sum beam interrupts	2572.2	2630.8	2805.2	2768.8	2463.2	2550.4	2268.2	3232.6

- *Ophthalmologic findings:* NE
- *Haematological findings:*

Table 104: Haematological data at D 29

	Males				Females			
Dose level (in ppm)	0	1500	3000	6500	0	1500	3000	6500
RBC (tera/L)	8.32	8.06	8.19	8.09	7.64	7.77	7.75	8.29**
Hb (mmol/L)	9.0	8.7	9.1	9.1	8.6	8.3	8.6	8.9
HT (L/L)	0.432	0.420	0.437	0.433	0.408	0.396	0.410	0.426
MCV (fL)	52.1	52.0	53.5	53.5	53.5	51.0	53.0	51.4
MCH (fmol)	1.08	1.08	1.11	1.13	1.12	1.07	1.11	1.08
MCHC (mmol/L)	20.77	20.71	20.76	21.03	20.90	21.03	20.88	20.96
Ret (%)	1.6	1.7	1.7	1.7	1.8	1.9	2.2	1.7
Plt (giga/L)	780	725	780	776	757	732	745	732
HQT (sec)	40.2	38.8	41.4	37.3*	36.1	35.4	35.3	36.1
WBC (giga/L)	7.75	6.57	6.40	6.81	4.87	5.15	4.70	5.24

- *Clinical biochemistry findings:*

Table 105: Enzyme and substrates data

	Males				Females			
Dose level (in ppm)	0	1500	3000	6500	0	1500	3000	6500
ALT (µkat/L)	0.69	0.72	0.78	0.86	0.59	0.60	0.71	0.52
AST (µkat/L)	1.86	1.68	1.86	1.85	1.56	1.64	2.31	1.59
ALP (µkat/L)	2.19	2.19	2.14	2.21	1.45	1.19	1.27	1.10
GGT_C (nkat/L)	0	0	0	0	0	0	0	1
Urea (mmol/L)	5.16	5.35	5.10	5.79	6.16	6.03	5.66	5.78
Crea (µmol/L)	23.4	22.7	21.5	22.2	27.3	27.7	26.6	24.5
Tot. prot (g/L)	60.33	60.01	60.53	59.95	61.48	61.32	62.48	60.70
Chol (mmol/L)	1.84	2.10	1.87	2.64*	1.43	1.60	1.54	2.00**

- *Gross pathology findings:* no treatment-related findings.
  - *In males:* 1 male of the lowest dose and 1 of the mid dose had focus on epididymides, while 1 male of the highest dose exhibited a kidney's dilatation.

- *In females:* 1 female of the lowest dose had kidney's pelvic dilatation, 1 of the mid dose had cyst on kidneys, while 1 of the highest dose had prominent acinar pattern in liver.

- *Organ weight:*

Table 106: Organ weight data (in mg, g or %)

		Males				Females			
Dose level (in ppm)		0	1500	3000	6500	0	1500	3000	6500
FBW (g)		271.08	271.0	255.58	269.22	174.58	171.66	177.9	174.68
Adrenal glands (mg)	Abs	61.0	59.8	68.4	73.8	66.2	68.2	77.6	82.2
	Rela	0.023	0.022	0.027	0.027	0.038	0.04	0.044	0.047
Brain (g)	Abs	2.02	2.064	1.994	1.994	1.86	1.796	1.844	1.778
	Rela	0.746	0.763	0.784	0.742	1.07	1.048	1.037	1.025
Heart (g)	Abs	0.906	0.874	0.846	0.87	0.62	0.64	0.648	0.632
	Rela	0.334	0.323	0.331	0.323	0.355	0.373	0.364	0.361
Kidneys (g)	Abs	2.036	2.016	1.968	2.212	1.382	1.326	1.42	1.42
	Rela	0.751	0.743	0.768	0.82	0.795	0.773	0.797	0.809
Liver (g)	Abs	6.986	7.25	6.946	7.856	4.738	4.636	5.124	4.996
	Rela	2.577	2.675	2.716*	2.914**	2.714	2.703	2.877	2.863
Spleen (g)	Abs	0.502	0.526	0.472	0.53	0.384	0.378	0.386	0.37
	Rela	0.185	0.193	0.188	0.197	0.22	0.22	0.217	0.211
Thymus (mg)	Abs	537.0	488.0	461.2	496.4	446.2	469.0	460.2	491.4
	Rela	0.197	0.18	0.18	0.183	0.256	0.274	0.259	0.281
Thyroid glands (mg)	Abs	19.8	16.8	19.0	19.4	14.8	14.8	14.0	15.4
	Rela	0.007	0.006	0.007	0.007	0.009	0.009	0.008	0.009
Epididymides (g)	Abs	0.72	0.7	0.684	0.722	-	-	-	-
	Rela	0.265	0.259	0.272	0.269	-	-	-	-
Prostate (g)	Abs	0.606	0.556	0.478	0.53	-	-	-	-
	Rela	0.223	0.204	0.188	0.198	-	-	-	-
Seminal vesicle (g)	Abs	0.716	0.682	0.532	0.68	-	-	-	-
	Rela	0.264	0.25	0.208	0.253	-	-	-	-
Testes (g)	Abs	3.206	3.124	3.022	3.416	-	-	-	-
	Rela	1.184	1.156	1.192	1.272	-	-	-	-
Ovaries (mg)	Abs	-	-	-	-	94.2	83.6	95.2	85.8
	Rela	-	-	-	-	0.054	0.049	0.054	0.05
Uterus (g)	Abs	-	-	-	-	0.478	0.636	0.614	0.388
	Rela	-	-	-	-	0.272	0.371	0.345	0.225

- *Histopathology findings:*

Table 107: Incidence and grading of the microscopic findings

		Males				Females			
Dose level (in ppm)		0	1500	3000	6500	0	1500	3000	6500
Adrenal cortex									
Accessory cortical tissue	Inc	0	1	1	0	0	1	1	0
Lipogenic pigmentation	Inc	0	0	0	0	0	0	1	0
Mineralization, (multi-)focal)	Inc	0	0	0	0	0	0	1	0

Vacuolation increased	Inc	0	0	1	1	0	0	0	1
Kidneys									
Dilatation, renal pelvis	Inc	0	0	0	1	1	1	1	0
Scar(s), cortical	Inc	0	0	0	0	0	0	1	0
Tubules, basophilic	Inc	0	0	0	2	4	0	0	5
Liver									
Fatty change, (multi-)focal/centrilobular	Inc	0	1	0	0	0	0	0	1
Hypertrophy, centrilobular	Inc	0	0	1	4	0	0	0	2
	Grade 1	-	-	1	4	-	-	-	1
	Grade 2	-	-	-	-	-	-	-	1
Mandibular glands									
Atrophy, diffuse	Inc	0	3	5	5	0	3	3	5
	Grade 1	-	2	3	1	-	2	2	2
	Grade 2	-	-	2	1	-	1	1	3
	Grade 3	-	1	-	2	-	-	-	-
	Grade 4	-	-	-	1	-	-	-	-
Nasal cavity I									
Degen./regen. olf. epith.	Inc	0	-	-	-	0	-	-	-
Nasal cavity II									
Degen./regen. olf. epith.	Inc	0	-	-	-	0	-	-	-
Nasal cavity III									
Degen./regen. olf. epith.	Inc	0	5	5	5	0	5	5	5
	Grade 1	-	4	-	-	-	3	2	-
	Grade 2	-	1	2	-	-	2	1	-
	Grade 3	-	-	3	3	-	-	2	2
	Grade 4	-	-	-	2	-	-	-	3
Epididymides									
Granuloma, spermatogenic	Inc	0	1	1	0	-	-	-	-
Ovaries									
Changes interstitial glands	Inc	-	-	-	-	0	-	-	1
Reduction functional bodies	Inc	-	-	-	-	0	-	-	1

3.12.1.3 Repeated-dose 28-day oral toxicity study in Wistar rats (Anonymous, 1997)

Study reference

Anonymous, 1997

Detailed study summary and results

Test type

GLP

4 weeks of exposure + 2 weeks of recovery

Test substance

- DMPP
- *Degree of purity:* 97.1 %

Test animals

- *Species/strain/sex:* Rat / Wistar / both sexes
- *Nb. of animals per sex per dose:* 5/sex/group for main groups + 5/sex/group for recovery group
- *Age and weight at the study initiation:* 49 d old, 212 to 245 g for males and 147 to 178 g for females

Administration/exposure

- *Route of administration:* oral, gavage
- *Duration and frequency of test/exposure period:* 28 days
- *Doses/concentration levels, rationale for dose level selection:* 0, 20, 100 and 500 mg/kg bw/d
- *Post exposure observation period:* 2 weeks for 2 additional groups (0 and 500 mg/kg bw/d)
- *Vehicle:* doubly distilled water

Results and discussion

- *Mortality and time to death (if occurring):* no mortality occurred during the study period.
- *Description, severity, time of onset and duration of clinical signs (reversible, irreversible, immediate, delayed):* ataxia was observed in all animals of the highest dose from day 3 in M and day 5 in F, 3-4 hours after daily treatment. Increase incidence of salivation and piloerection. All clinical findings were observed after gavage a,d were reversible until the next administration.
- *Body weight and body weight changes:*

Table 108: Body weight data (in g)

	Males						Females					
	Main groups				Recovery groups		Main groups				Recovery groups	
Dose level (in mg/kg bw/d)	0	20	100	500	0	500	0	20	100	500	0	500
D 0	229.8	228.1	228.3	230.0	228.7	229.5	159.8	170.8	163.7	163.4	161.7	157.4
D 7	277.6	275.9	274.0	279.0	281.0	274.6	176.2	186.7	176.9	184.2	177.5	176.1
D 14	315.6	274.0	315.4	317.8	317.2	313.2	190.1	202.4	187.9	195.2	190.4	197.8
D 21	345.0	340.6	346.2	351.7	347.5	341.4	197.1	213.2	195.7	209.3	198.3	209.2
D 28	355.6	359.9	360.0	366.1	362.4	353.7	207.5	222.6	209.6	221.9	206.1	219.9
D 35	-	-	-	-	385.9	371.5	-	-	-	-	221.0	225.4
D 42	-	-	-	-	406.7	390.7	-	-	-	-	227.2	230.0
BWG D 0 to 28	125.8	131.8	131.8	136.1	133.7	124.2	47.8	51.7	45.9	58.5	44.4	62.5*
BWG D 0 to 42	-	-	-	-	178.0	161.2	-	-	-	-	65.5	72.6

- *Food/water consumption:*

Table 109: Mean food consumption (in g/animal/day)

	Males						Females					
	Main groups				Recovery groups		Main groups				Recovery groups	
Dose level (in mg/kg bw/d)	0	20	100	500	0	500	0	20	100	500	0	500
D 7	26.8	26.8	26.4	26.6	27.2	26.7	17.1	19.0	17.6	17.8	17.9	17.8
D 14	28.1	28.1	27.4	29.1	27.7	28.9	18.0	19.3	17.7	18.0	18.0	19.1

D 21	27.5	27.0	27.5	30.4**	27.8	29.1	17.8	19.5	18.2	18.9	18.4	19.8
D 28	24.4	25.0	24.4	26.7	24.9	25.3	17.1	18.2	17.7	18.5	17.5	19.0
D 35	-	-	-	-	26.7	24.3	-	-	-	-	18.4	18.1
D 42	-	-	-	-	25.5	24.4	-	-	-	-	17.4	17.1

- *Sensory activity, grip strength and motor activity assessments (when available):* no tremors or abnormal movements observed.

Table 110: Sensory activity, grip strength and motor activity data

		Males						Females					
		Main groups				Recovery groups		Main groups				Recovery groups	
Dose level (in mg/kg bw/d)		0	20	100	500	0	500	0	20	100	500	0	500
Mean rearing	D 28	3.4	5.4	2.2	4.0	2.8	11.2**	4.8	3.4	4.2	7.6	1.6	6.0
	D 42	-	-	-	-	4.2	4.8	-	-	-	-	6.6	11.0
Grip strength forelimbs													
GS F (Newton)	D 28	3.8	4.0	4.0	3.7	4.0	4.0	6.5	6.4	7.0	6.6	6.4	5.7
	D 42	-	-	-	-	5.4	6.4	-	-	-	-	7.0	6.9
Grip strength hindlimbs													
GS F (Newton)	D 28	3.3	2.7	3.0	2.4	2.8	2.2	4.9	4.4	4.4	4.7	4.6	4.2
	D 42	-	-	-	-	3.2	3.6	-	-	-	-	4.6	4.2
Landing foot splay test													
FST (cm)	D 28	13.0	13.2	13.1	13.6	13.2	12.7	11.0	10.4	9.5	10.6	10.5	10.5
	D 42	-	-	-	-	13.4	12.6	-	-	-	-	10.6	9.9
Motor activity													
Beam interr.	D 28	245	287	214	149	267	173**	298	319	330	194	295	252
	D 42	-	-	-	-	91	92	-	-	-	-	252	251
Open field observation													
Impairment of gait (Inc.)	D 2	0	0	0	0	0	0	0	0	0	0	0	0
	D 7	0	0	0	2	0	2	0	0	0	3	0	2
	D 21	0	0	1	5	0	5	0	0	0	5	0	4
	D 35	-	-	-	-	0	0	-	-	-	-	0	0

- *Ophthalmologic findings:* NE
- *Haematological findings:*

Table 111: Haematological data

		Males						Females					
		Main groups				Recovery groups		Main groups				Recovery groups	
Dose level (in mg/kg bw/d)		0	20	100	500	0	500	0	20	100	500	0	500
RBC (tera/L)	D 29	8.32	8.34	8.06	8.35	8.44	7.51	7.65	8.05	7.87	7.94	8.03	7.96
	D 43	-	-	-	-	8.58	8.19	-	-	-	-	8.08	8.05
Hb (mmol/L)	D 29	9.6	9.6	9.4	9.8	9.6	8.9	8.9	9.3	9.2	9.3	9.3	9.4
	D 43	-	-	-	-	9.5	9.7	-	-	-	-	9.4	9.5
Ht (L/L)	D 29	0.426	0.426	0.412	0.436	0.425	0.388	0.388	0.405	0.401	0.402	0.400	0.406
	D 43	-	-	-	-	0.426	0.429	-	-	-	-	0.415	0.415
MCV (fL)	D 29	51.3	51.1	51.2	52.2	50.4	51.7	50.7	50.3	50.9	50.6	49.8	51.0
	D 43	-	-	-	-	49.6	52.4	-	-	-	-	51.4	51.6

MCH (fmol)	D 29	1.16	1.16	1.16	1.18	1.14	1.18	1.17	1.16	1.17	1.18	1.15	1.18
	D 43	-	-	-	-	1.11	1.19	-	-	-	-	1.17	1.18
MCHC (mmol/L)	D 29	22.6	22.7	22.63	22.62	22.65	22.76	23.03	22.92	22.92	23.38	23.16	23.07
	D 43	-	-	-	-	22.3	22.69	-	-	-	-	22.74	22.94
Plt (giga/L)	D 29	871	869	855	919	832	829	925	862	846	893	856	950
	D 43	-	-	-	-	825	854	-	-	-	-	905	990
WBC (giga/L)	D 29	8.35	9.42	7.60	9.85	7.94	9.13	4.86	5.80	4.61	5.78	4.77	4.75
	D 43	-	-	-	-	9.42	9.07	-	-	-	-	5.50	5.12
HQT (sec)	D 29	31.5	31.4	31.0	32.1	31.9	29.9	30.1	29.5	28.9	28.4	28.2	28.1
	D 43	-	-	-	-	32.5	31.8	-	-	-	-	24.7	23.9

- *Clinical biochemistry findings:*

Table 112: Biological data

		Males						Females					
		Main groups				Recovery groups		Main groups				Recovery groups	
Dose level (in mg/kg bw/d)		0	20	100	500	0	500	0	20	100	500	0	500
ALT (µkat/L)	D 29	0.78	0.9	0.9	1.18	0.8	1.09	0.66	0.72	0.79	0.77	0.68	0.73
	D 43	-	-	-	-	0.99	0.72	-	-	-	-	0.6	0.6
AST (µkat/L)	D 29	1.98	2.12	2.04	2.07	1.78	2.1	1.81	1.95	2.13	1.79	1.62	1.67
	D 43	-	-	-	-	1.61	1.76	-	-	-	-	1.46	1.96
ALP (µkat/L)	D 29	4.07	5.14	4.46	5.13	4.98	4.09	2.95	3.57	3.3	3.1	2.82	3.77
	D 43	-	-	-	-	4.35	3.65	-	-	-	-	2.55	2.98
SGGT (nkat/L)	D 29	0	1	1	1	0	3	5	8	10	14**	8	5
	D 43	-	-	-	-	10	12	-	-	-	-	15	12

- *Gross pathology findings:*
  - *Main groups:* 1 female of the low dose group exhibited an uterus's dilatation and 1 female of the mid dose group had a thickening of wall (glandular stomach). Other animals did not exhibited abnormalities.
  - *Recovery groups:* No abnormalities observed.
- *Organ weight:*
  - *Males:*

Table 113: Organ weight in males (in mg, g or %)

		Main groups				Recovery groups	
Dose level (in mg/kg bw/d)		0	20	100	500	0	500
FBW (g)		323.1	328.72	330.64	331.92	374.08	357.32
Adrenal glands (mg)	Abs	95.6	89.6	90.6	132.8**	89.4	105.4
	Rela	0.03	0.027	0.027	0.04**	0.024	0.03
Brain (g)	Abs	1.946	1.956	1.98	1.952	2.068	1.986
	Rela	0.605	0.596	0.601	0.589	0.553	0.557
Heart (g)	Abs	1.198	1.242	1.264	1.298	1.278	1.212
	Rela	0.372	0.378	0.383	0.392	0.341	0.339
Kidneys (g)	Abs	2.552	2.51	2.674	2.716	2.488	2.602

	Rela	0.79	0.765	0.812	0.819	0.666	0.729
Liver (g)	Abs	11.33	11.779	11.792	13.696*	12.542	12.466
	Rela	3.5	3.576	3.558	4.127**	3.35	3.478
Spleen (g)	Abs	0.666	0.682	0.668	0.764	0.768	0.684
	Rela	0.206	0.209	0.201	0.231	0.205	0.191
Thymus (mg)	Abs	443	402	456.6	533	415.6	409.6
	Rela	0.139	0.121	0.137	0.161	0.111	0.115
Epididymides (g)	Abs	0.922	0.894	0.93	0.832	1.188	0.968**
	Rela	0.287	0.273	0.282	0.251	0.318	0.272**
Testes (g)	Abs	3.372	3.318	3.138	3.028	3.4	3.334
	Rela	1.051	1.012	0.949	0.914	0.909	0.936

- *Females:*

Table 114: Organ weight in females (in mg, g or %)

		Main groups				Recovery groups	
Dose level (in mg/kg bw/d)		0	20	100	500	0	500
FBW (g)		191.38	203.16	190.34	203.22	206.12	208.66
Adrenal glands (mg)	Abs	108	99.6	101.6	115.8	94.8	108.6
	Rela	0.057	0.049	0.053	0.057	0.046	0.052
Brain (g)	Abs	1.74	1.786	1.756	1.788	1.786	1.814
	Rela	0.916	0.88	0.922	0.883	0.87	0.873
Heart (g)	Abs	0.81	0.82	0.82	0.848	0.886	0.848
	Rela	0.425	0.403	0.431	0.417	0.431	0.406
Kidneys (g)	Abs	1.67	1.798	1.72	1.874	1.746	1.694
	Rela	0.876	0.886	0.904	0.922	0.847	0.813
Liver (g)	Abs	5.816	6.324	6.354	7.596*	6.49	6.828
	Rela	3.043	3.11	3.338	3.729**	3.153	3.269
Spleen (g)	Abs	0.44	0.432	0.472	0.444	0.48	0.5
	Rela	0.23	0.212	0.248	0.218	0.234	0.238
Thymus (mg)	Abs	283.8	298.2	262.8	310.4	262.4	281.6
	Rela	0.146	0.148	0.138	0.153	0.127	0.136
Ovaries (mg)	Abs	101.2	103.4	93	107.2	96.8	97.8
	Rela	0.053	0.051	0.049	0.053	0.047	0.047

- *Histopathology findings:* nasal cavity not examined.

  For recovery groups, only adrenal glands were examined.

Table 115: Microscopic findings

		Males				Females			
		Main groups				Main groups			
Dose level (in mg/kg bw/d)		0	20	100	500	0	20	100	500
Adrenal cortex									
Hypertrophy	Inc	0/5	0/5	0/5	5/5	0/5	NE	NE	0/5
	Grade 2	-	-	-	5	-	-	-	-
Forestomach									

Malformation of the glandular stomach	Inc	0/5	NE	NE	0/5	0/5	NE	1/1	0/5
Thymus									
Haemorrhage	Inc	3/5	NE	NE	5/5	2/5	NE	NE	1/5
	Grade 1	-	-	-	1	2	-	-	1
	Grade 2	3	-	-	3	-	-	-	-
	Grade 3	-	-	-	1	-	-	-	-
Uterus									
Dilatation	Inc	-	-	-	-	1/5	1/1	NE	1/5

3.12.1.4 Subchronic oral toxicity study in Wistar rats (Anonymous, 2003)

Study reference

Anonymous, 2003

Detailed study summary and results

Test type

OECD TG 408

GLP

Test substance

- DMPP
- *Degree of purity:* 97.1 %

Test animals

- *Species/strain/sex:* Rat / Wistar / both sexes
- *Nb. of animals per sex per dose:* 10/sex/group
- *Age and weight at the study initiation:* 42 ± 1 days old

Administration/exposure

- *Route of administration:* oral, diet
- *Duration and frequency of test/exposure period:* 3 months, daily
- *Doses/concentration levels, rationale for dose level selection:* 0, 200, 1000 and 5000 ppm
- *Post exposure observation period:* /
- *Vehicle:* /
- *Actual dose (mg/kg bw/day) and conversion factor from diet/drinking water test substance concentration (ppm) to the actual dose, if applicable:*
    - *Males:* 0, 13.6, 69.2 and 353.8 mg/kg bw/d
    - *Females:* 0, 16.5, 82.1 and 400.7 mg/kg bw/d

Results and discussion

- *Mortality and time to death (if occurring):* no mortality occurred during the study period.
- *Description, severity, time of onset and duration of clinical signs (reversible, irreversible, immediate, delayed):* no treatment-related effects.

- *Body weight and body weight changes:*

Table 116: Body weight (g)

	Males				Females			
Dose level (in ppm)	0	200	1000	5000	0	200	1000	5000
D 0	149.0	150.2	148.9	147.8	123.1	121.7	120.6	123.2
D 7	188.9	189.5	185.8	180.3	140.2	138.2	141.0	134.7
D 28	285.9	281.0	274.5	269.7	182.4	179.7	172.5	182.2
D 49	342.3	336.6	324.4	312.5	202.5	200.7	190.8	201.8
D 63	364.8	356.9	344.4	331.0	212.2	209.6	198.9	207.6
D 77	381.9	371.9	364.2	345.5	218.2	217.5	202.8	215.4
D 91	390.7	377.9	372.1	351.8	220.1	218.5	202.8*	215.7
BWG D 0 to 91	241.6	227.7	223.2	204.0*	97.0	96.8	82.2*	92.5

- *Food/water consumption:*

Table 117: Food consumption (g/animal/day)

	Males				Females			
Dose level (in ppm)	0	200	1000	5000	0	200	1000	5000
D 7	19.6	19.4	19.4	17.0**	15.5	16.9	17.7	16.2
D 35	21.4	21.2	21.0	20.7	16.9	16.1	14.8*	15.9
D 63	21.4	20.7	20.2	20.6	16.5	16.0	14.9*	15.1
D 91	22.3	18.8**	18.3**	18.2**	14.3	14.2	12.9*	13.3

- *Sensory activity, grip strength and motor activity assessments (when available):*
  - *Home cage observation:* no tremors, convulsions or impairment of gait observed.
  - *Sensorimotor tests/reflexes:* no treatment-related effects.
  - *FOB:*

Table 118: FOB

	Males				Females			
Dose level (in ppm)	0	200	1000	5000	0	200	1000	5000
Rear	7.5	3.6	4.3	6.1	12.0	11.6	14.4	11.9
FST (cm)	12.5	12.0	12.5	11.6	10.8	9.9	9.5	10.3
GSF (Newton)	8.7	8.5	8.7	8.7	7.8	8.1	7.9	7.2
GSH (Newton)	4.2	4.2	4.1	3.6	3.6	3.7	3.3	3.4
Sum interr. interv 1-12	314.5	341.9	307.0	267.7	314.7	298.2	300.4	296.5

- *Haematological findings:*

Table 119: Haematological data

	Males				Females			
Dose level (in ppm)	0	200	1000	5000	0	200	1000	5000
RBC (tera/L)	8.22	8.23	8.18	8.50	7.73	7.75	7.72	7.90
Hb (mmol/L)	9.0	9.0	9.1	9.6*	8.9	8.9	8.8	9.1
Ht (L/L)	0.422	0.423	0.426	0.443	0.420	0.416	0.415	0.418

MCV (fL)	51.4	51.4	52.1	52.2	54.4	53.8	53.7	53.0
MCH (fmol)	1.10	1.10	1.12	1.13	1.15	1.15	1.15	1.16
MCHC (mmol/L)	21.40	21.38	21.48	21.62	21.19	21.47	21.29	21.76*
Plt (giga/L)	682	699	653	604*	626	659	695	689
WBC (giga/L)	5.60	5.39	5.45	5.57	2.55	3.45**	2.79	4.59**
HQT (sec)	31.4	31.6	30.8	30.9	28.3	27.8	28.1	29.9

- *Clinical biochemistry findings:*

Table 120: biological data

	Males				Females			
Dose level (in ppm)	0	200	1000	5000	0	200	1000	5000
ALT (µkat/L)	0.63	0.54	0.63	0.98*	0.73	0.66	0.74	0.52
AST (µkat/L)	1.65	1.75	2.20	2.13	3.87	2.26	2.12	1.81
ALP (µkat/L)	3.34	3.50	3.68	3.11	1.84	1.90	2.11	2.00
SGGT (nkat/L)	3	4	1	4	9	12	8	12

- *Gross pathology findings:* no treatment-related findings.
- *Organ weight:*

Table 121: Organ weight (in mg, g or %)

		Males				Females			
Dose level (in ppm)		0	200	1000	5000	0	200	1000	5000
FBW (g)		362.8	349.68	344.21	321.9	201.86	199.36	187.65	200.51
Adrenal glands (mg)	Abs	60.2	63.7	64.0	70.0	74.4	69.3	68.0	80.5
	Rela	0.017	0.018	0.019	0.022**	0.037	0.035	0.036	0.04
Brain (g)	Abs	1.988	1.968	1.975	1.93	1.823	1.806	1.809	1.803
	Rela	0.552	0.568	0.576	0.606	0.906	0.908	0.967	0.903
Heart (g)	Abs	1.025	0.98	0.991	0.974	0.745	0.741	0.709	0.734
	Rela	0.283	0.281	0.289	0.303	0.37	0.372	0.377	0.366
Kidneys (g)	Abs	2.168	2.215	2.234	2.394	1.424	1.39	1.489	1.527
	Rela	0.6	0.636	0.651	0.744**	0.709	0.698	0.793	0.762*
Liver (g)	Abs	8.662	8.24	8.122	8.522	5.032	4.848	5.089	5.631*
	Rela	2.387	2.356	2.355	2.642**	2.496	2.432	2.711	2.806**
Spleen (g)	Abs	0.621	2.215	2.234	2.394	0.399	0.39	0.385	0.419
	Rela	0.171	0.163	0.163	0.167	0.198	0.196	0.205	0.208
Thymus (mg)	Abs	273.2	293.3	292.1	287.3	250.1	254.2	237.3	283.7
	Rela	0.074	0.085*	0.085*	0.089*	0.124	0.128	0.125	0.141
Epididymides (g)	Abs	1.04	1.076	1.068	0.979	-	-	-	-
	Rela	0.288	0.31	0.311	0.308	-	-	-	-
Testes (g)	Abs	3.289	3.422	3.38	3.171	-	-	-	-
	Rela	0.912	0.983	0.983	0.991	-	-	-	-
Ovaries (mg)	Abs	-	-	-	-	91.6	87.4	89.4	92.8
	Rela	-	-	-	-	0.045	0.044	0.047	0.046

- *Histopathology findings:*

Table 122: Microscopic data

		Males				Females			
Dose level (in ppm)		0	200	1000	5000	0	200	1000	5000
Adrenal cortex									
Extracortical tissue	Inc	0/10	1/10	0/10	0/10	0/10	2/10	1/10	1/10
Nasal cavity, level III									
Disarrangement	Inc	0/10	0/10	8/10	10/10	0/10	0/10	9/10	10/10
	Grade 1	-	-	8	-	-	-	9	-
	Grade 2	-	-	-	7	-	-	-	3
	Grade 3	-	-	-	3	-	-	-	7
Pancreas									
Focal degeneration	Inc	1/10	NE	NE	2/10	0/10	NE	NE	1/10
Liver									
Minimal centrolobular hypertrophy	Inc	0/10	NE	NE	5/10	0/10	NE	NE	5/10

The “disarrangement” of the olfactory epithelium resulted from degenerative and regenerative processes and was located in the dorsal part of the nasal septum and the ethmoid turbinate.

3.12.2 Human data

No human data available

3.12.3 Other data

No other data available.

3.13 Aspiration hazard

Hazard class not assessed in this dossier.

4 ENVIRONMENTAL HAZARDS

Not evaluated in this CLH dossier.

5 ABBREVIATIONS

*: $p < 0.05$

**: $p < 0.01$

Abs: absolute

ALD: aldosterone

ALP: alkaline phosphatase

ALT: alanine aminotransferase

Approx.: approximately
AST: aspartate aminotransferase
ATE: acute toxicity estimate
Bw: body weight
Bwg: body weight gain
Ca: calcium
CC: corticosterone
Chol: cholesterol
Crea: creatinine
D: day
Degen.: degenerative
DPC: day post-coitum
DPP: day post-partum
E_2: estradiol
Epith: epithelium
Exp: experiment
F: female
FBW: final body weight
FOB: Functional Observational Battery
FST: landing foot-splay test
FSH: follicle-stimulating hormone
GD: gestation day
GGT_C: serum-γ-glutamyltransferase
GLDH: Glutamate Dehydrogenase
GLP: good laboratory practice
GS F: grip strength forelimbs
GS H: grip strength hindlimbs
Hb: hemoglobin
HCD: historical control data
HQT: prothrombin time (Hepato Quick's test)
Ht: hematocrit
Inc: incidence
INP: inorganic phosphate
Interr.: beam interrupts
Interv.: interval
LC50: lethal concentration 50%
LD: lactation day

LD50: lethal dose 50 %

LH: luteinizing hormone

M: male

MCH: mean corpuscular hemoglobin

MCHC: mean corpuscular hemoglobin concentration

MCV: mean corpuscular volume

Min: minimum

MMAD: mass median aerodynamic diameter

Nb: number

NE: not examined

NT: not tested

NZW: New Zealand White

Olf.: olfactive

PC: positive control

Plt: platelet

PND: post-natal day

PTH: parathyroid hormone

RBC: red blood cell

Regen.: regenerative

Rela: relative

Resp: respectively

Ret: reticulocyte

St. Dev: standard deviation

SGGT: serum-γ-glutamyltransferase

Sign: significant

T: testosterone

TG: test guideline

Tot.: total

Tot. prot.: total protein

Trig: triglycerides

Vit: vitamin

W: week

WBC: white blood cell