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:

3,5-dimethylpyrazole

EC Number: **200-657-5**

CAS Number: **67-51-6**

Index Number: **/**

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Hazard class not assessed in this 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 (Anonymous, 1994)

Study reference

Anonymous, 1994

Detailed study summary and results

Test type

Similar to OECD TG 401

GLP

Test substance

- 3,5-dimethylpyrazole
- *Degree of purity :* > 99%

Test animals

- *Species/strain/sex :* rat / SD / both sexes
- *Nb. of animals per sex per dose :* 5 females for the low and mid dose groups.
  5 males and 5 females for the highest dose.
- *Age and weight at the study initiation :* 4 to 7 weeks of age and 96 to 119 g

Administration/exposure

- *Mode of administration :* oral, gavage
- *Duration of test/exposure period :* single exposure
- *Doses/concentration levels :* 1260, 1600 and 2000 mg/kg bw (no control group)
- *Post exposure observation period :* 15 days
- *Vehicle :* aqueous methylcellulose

Results and reliability

- *LD_{50} value with confidence limits if calculated :* 1717 mg/kg bw in females

- *Nb of deaths at each dose level :* 2 females died at 1600 mg/kg bw and 2 males and 4 females died at 2000 mg/kg bw.

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

- *Time of death :* 2 females of the highest dosed died the first day (after 3 and 4 hours), 2 females of the mid dose and 2 males and 2 females of the highest dose died on day 2.
- *Clinical signs* : pallor of extremities and decreased respiratory rate in all animals.

  Abnormal carriage (in all females at 1260 mg/kg bw + 3 females at 1600 mg/kg bw + 4 males and 3 females at 2000 mg/kg bw), abnormal gait (in 3 males and 2 females at 2000 mg/kg bw), lethargy (in all females at 1260 mg/kg bw + 4 females at 1600 mg/kg bw + 5 males and 3 females at 2000 mg/kg bw), increased salivation (in all females at 1260 mg/kg bw + 1 male at 2000 mg/kg bw) and unsteadiness (in 5 females at 1260 mg/kg bw +3 females at 1600 mg/kg bw + 2 males and 4 females at 2000 mg/kg bw), prostration (in 2 males and 3 females at 2000 mg/kg bw).

  Recovery was complete by either 3 days, 4 days and 5 days, resp. at 1260, 1600 and 2000 mg/kg bw.
- *Body weight :* slightly decrease on day 8 for 1 female at 1260 mg/kg bw and for 3 males and 1 female at 2000 mg/kg bw.
- *Necropsy findings, including doses affected, severity and nb of animals affected :* no treatment-related *effect observed.*

  At 1600 mg/kg bw, one female, which died, had darkened appearance to the spleen and kidney cortex.

  All dead animals exhibited thickening of the stomach walls and fluid contents in the stomach and intestines.

3.1.1.2 Acute oral toxicity study (Anonymous, 1976)

Study reference

Anonymous, 1976

Detailed study summary and results

Test type

No guideline followed

GLP : unspecified

Test substance

- 3,5-dimethylpyrazole
- *Degree of purity :* unspecified

Test animals

- *Species/strain/sex :* rat / strain not specified / both sexes

- *Nb. of animals per sex per dose :* 5 animals per dose (exact distribution of males and females not specified)
- *Age and weight at the study initiation :* young adult, 200 to 300 g

Administration/exposure

- *Mode of administration (gavage, in diet, other) :* oral, gavage
- *Duration of test/exposure period :* single exposure
- *Doses/concentration levels, rationale for dose level selection :* 0.5, 1.0, 2.0, 4.0, 8.0 and 16.0 g/kg bw (no control group)
- *Post exposure observation period :* 14 days
- *Vehicle :* propylene glycol

Results and reliability

- *LD_{50} value with confidence limits if calculated :* 2140 mg/kg bw
- *LD_0 :* 1000 mg/kg bw
- *Nb of deaths at each dose level :* ≥ 4.0 g/kg bw : all animals died

  2.0 g/kg bw : 2 on 5 animals died

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) :* all animals treated ≥ 4.0 g/kg bw died on day 1 (animals exposed to 8.0 and 16.0 g/kg bw died within one hour).

  At 2.0 g/kg bw, 2 on 5 animals died (one on day 2 and one on day 5).

  Animals treated with ≤ 1.0 g/kg bw survived until day 14.
- *Clinical signs :* all animals exhibited unkempt coats.

  At 1.0 g/kg bw : animals were languid + slight diarrhoea. Recovery within 5 day.

  At 2.0 g/kg bw : lethargy, hematuria, slight nasal haemorrhage, diarrhoea + swelling of the neck and cranium after 6 day.

  ≥ 4.0 g/kg bw : laboured breathing and lethargy proceeded comas and death.
- *Necropsy findings, including doses affected, severity and nb of animals affected:* only performed on dead animals. (No more information)

3.1.1.3 Acute oral toxicity study (Dewitt J.B. *et al.*, 1953)

Study reference

Dewitt J.B. *et al.*, 1953, Relationship between chemical structure and toxic action on rats, Chemical biological coordination centre, review no. 5 national research council, Washington D.C.

Detailed study summary and results

Test type

No information about guidelines or methods

No GLP compliance

Test substance

- 3,5-dimethylpyrazole
- *Degree of purity :* unspecified

Test animals

- *Species/strain/sex :* rat / strain unspecified / sex unspecified
- *Nb. of animals per sex per dose :* no information available
- *Age and weight at the study initiation :* no information available

Administration/exposure

- *Mode of administration (gavage, in diet, other) :* oral (no more information)
- *Duration of test/exposure period :* no information available
- *Doses/concentration levels :* no information available
- *Post exposure observation period :* no information available
- *Vehicle :* unspecified

Results and reliability

- *LD_{50} value with confidence limits if calculated :* > 500 mg/kg bw
- *Nb of deaths at each dose level :* unspecified

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) :* unspecified
- *Clinical signs :* unspecified
- *Necropsy findings, including doses affected, severity and nb of animals affected :* unspecified

3.1.1.4 Acute oral toxicity study (Anonymous, 2009)

Study reference

Anonymous, 2009

Detailed study summary and results

Test type

No information about guidelines or methods

GLP compliance : unspecified

Test substance

- 3,5-dimethylpyrazole
- *Degree of purity :* unspecified

Test animals

- *Species/strain/sex :* mouse / strain unspecified / sexe unspecified
- *Nb. of animals per sex per dose :* unspecified
- *Age and weight at the study initiation :* unspecified

Administration/exposure

- *Mode of administration (gavage, in diet, other) :* oral (no more information available)
- *Duration of test/exposure period :* unspecified
- *Doses/concentration levels :* unspecified
- *Post exposure observation period :* unspecified
- *Vehicle :* unspecified

Results and reliability

- *LD_{50} or LC_{50} value with confidence limits if calculated :* 1060 mg/kg bw
- *Nb of deaths at each dose level :* no information available

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) :* no information available
- *Clinical signs :* ataxia + general anesthetic (no more information available)
- *Necropsy findings, including doses affected, severity and nb of animals affected :* no information available

3.1.1.5 Acute oral toxicity study (Anonymous, 2007)

Study reference

Anonymous, 2007

Detailed study summary and results

Test type

No information about guidelines or methods

GLP compliance : unspecified

Test substance

- 3,5-dimethylpyrazole
- *Degree of purity :* unspecified

Test animals

- *Species/strain/sex :* rat and mouse / strain unspecified / sex unspecified
- *Nb. of animals per sex per dose :* unspecified
- *Age and weight at the study initiation :* unspecified

Administration/exposure

- *Mode of administration (gavage, in diet, other) :* oral (no more information available)
- *Duration of test/exposure period :* unspecified
- *Doses/concentration levels, rationale for dose level selection :* unspecified
- *Post exposure observation period :* unspecified
- *Control group and treatment :* unspecified
- *Vehicle :* unspecified

Results and reliability

- *LD_{50} or LC_{50} value with confidence limits if calculated :* > 2140 mg/kg bw in rat
  > 500 mg/kg bw in mouse
- *Nb of deaths at each dose level :* no information available

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) :* no information available
- *Clinical signs :* no information available
- *Necropsy findings, including doses affected, severity and nb of animals affected :* no information available

3.1.1.6 Acute oral toxicity study (Anonymous, 2008)

Study reference

Anonymous, 2008

Detailed study summary and results

Test type

No information about guidelines or methods

GLP compliance : unspecified

Test substance

- 3,5-dimethylpyrazole
- *Degree of purity :* unspecified

Test animals

- *Species/strain/sex :* mouse / strain unspecified / sex unspecified
- *Nb. of animals per sex per dose :* unspecified
- *Age and weight at the study initiation :* unspecified

Administration/exposure

- *Mode of administration (gavage, in diet, other) :* oral (no more information)
- *Duration of test/exposure period :* unspecified
- *Doses/concentration levels, rationale for dose level selection :* unspecified
- *Post exposure observation period :* unspecified
- *Vehicle :* unspecified

Results and reliability

- *LD_{50} or LC_{50} value with confidence limits if calculated :* 1060 mg/kg bw
- *Nb of deaths at each dose level :* no information available

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) :* no information available
- *Clinical signs :* no information available
- *Necropsy findings :* no information available

3.1.2 Human data

No human data available

3.1.3 Other data

No other data available

3.2 Acute toxicity - dermal route

Hazard class not assessed in this dossier

3.3 Acute toxicity - inhalation route

No study 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

Hazard class not assessed in this dossier

3.7 Skin sensitisation

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 Extended One-Generation reproductive toxicity study (Anonymous, 2020)

Study reference

Anonymous, 2020

Detailed study summary and results

Test type

OECD TG 443 (10 weeks prior to pairing (sexual maturity was attained during the pre-pairing phase and animals were sexually mature by the time of pairing for mating))

GLP

Test substance

- 3,5-dimethylpyrazole
- *Degree of purity :* 99.98 %

Test animals

- *Species/strain/sex :* Rat / Wistar / both sexe
- *Nb. of animals per sex per dose :*
    - F0 generation : 25/sex/group
    - Cohort 1A : 20/sex/group
    - Cohort 1B : 20/sex/group
    - Cohort 2A : 10/sex/group
    - Cohort 2B : 10/sex/group
    - Cohort 3 : 10/sex/group
- *Age and weight at the study initiation :* 6 weeks old, 125.8 to 234.7 g in males and 116.8 to 182.2 g in females.

Administration/exposure

- *Route of administration :* oral, gavage
- *Duration and frequency of test/exposure period :* daily

- F0 generation : for males up to 127 days (10 weeks prior mating, during pairing and until 42/43 days post-pairing) and for females up to 122 days (10 weeks prior pairing, during pairing and gestation, until lactation days 21).
- F1 pups were dosed from PND 14 to 21.
- Cohort 1A : up to 73 days.
- Cohort 1B : up to 75 days prior pairing, through pairing and until lactation day 4 for females and up to 96 days in males.
- Cohort 2A : up to 56 days.
- Cohort 2B : for 1 day.
- Cohort 3 : up to 62 days.

- *Doses/concentration levels :* 0, 20, 50 and 100 mg/kg bw/d (high dose anticipated to induce minimal parental toxicity without causing death or affecting parturition, pup growth, or mating of the first generation).
- *Vehicle :* propylene glycol

Results and discussion

For F0 generation (per dose):

- *Nb of animals at the start of the test and mating :*
  - *In males :* at the start of the test : 25 animals in all dose groups

    At the start of mating : 24, 24, 25 and 25 males, resp. at 0, 20, 50 and 100 mg/kg bw/d.

    At the start of the post-pairing period : 24, 24, 25 and 25 males, resp. at 0, 20, 50 and 100 mg/kg bw/d.
  - *In females :* at the start of the test : 25 animals in all dose groups

    At the start of gestation period : 24, 23, 24 and 23 pregnant females, resp. at 0, 20, 50 and 100 mg/kg bw/d.
- *Time of death during the study and whether animals survived to termination :* one male was found dead on study day 5 in control group, one male of the low dose group was found dead on study day 2 and one male of the highest dose was found dead on study day 107. While in female, one animal of the highest dose was sent to necropsy on lactation day 2 due to total litter loss.
- *Clinical observations :* few animals exhibited increase salivation at the mid and high dose groups and sometimes in the control and low dose groups.
- *Body weight data :*
  - *In males :*

Table 1 : Body weight in males (in g)

Dose level (in mg/kg bw/d)	0	20	50	100
Pre-pairing period				
D 1	164.0	162,5	164,8	165,2

D 22	273,4	273,6	278,1	275,5
D 43	339,1	343,3	351,8	346,2
D 71	389,4	395,1	405,3	396,9
Pairing period				
D 7	392,6	398,2	409,0	402,4
D 14	405,6	411,5	424,0	412,6
Post-pairing period				
D 8	416,0	423,0	433,2	420,6
D 29	436,6	444,8	454,7	442,4
D 43	436,4	449,5	457,8	439,8

- *In females :*

Table 2 : Body weight in females (in g)

Dose level (in mg/kg bw/d)	0	20	50	100
Pre-pairing period				
D 1	141,6	141,1	144,5	139,8
D 22	192,0	191,8	195,1	193,1
D 43	220,5	223,3	226,5	221,8
D 71	241,9	244,0	248,6	239,4
Gestation period				
D 0	241,5	245,0	248,4	240,0
D 10	271,5	277,8	282,1	274,7
D 20	346,9	351,3	356,6	349,1
Lactation period				
D 1	268,7	272,4	277,2	270,5
D 7	297,2	297,0	300,0	290,4
D 21	297,3	299,3	307,1	296,2

- *Food consumption :*
  - *In males :* sign. higher in males exposed to the highest dose during post-pairing period (D 4-8, D 11-15, D 18-22, D 22-25, D 25-29, D 32-36 and D 36-39 of the post-pairing period).
  - *In females :* sign. higher at :

    The mid and high dose group during the GD 7-8 and at LD 6-7

    The highest dose during GD 9-10, GD 12-13

    The mid dose during GD 10-11 and at LD 9-10

    The low dose during LD 6-7
- *Haematological findings :*

Table 3 : Haematological data

	Males (at post-pairing day 43)				Females (at LD 22)			
Dose level (in mg/kg bw/d)	0	20	50	100	0	20	50	100
Hb (g/dL)	15.0	14.4*	14.2**	14.2**	15.6	15.6	15.3	15.1
RBC (10^{12}/L)	8.74	8.23*	8.16**	7.64***	8.11	8.13	7.50*	6.99***
PCV (%)	44.8	42.3**	42.8*	42.9*	47.3	47.5	45.4	45.9
MCV (fL)	51.0	51.5	52.4*	56.3***	58.3	58.4	60.7*	65.7***
MCH (pg)	17.1	17.6	17.4	18.7***	19.3	19.3	20.4*	21.6***

MCHC (g/dL)	33.6	34.1	33.3	33.2	33.0	33.0	33.6	33.0
Ret (%)	2.1	2.3	2.6**	3.0***	2.4	2.4	3.4	3.5
RDW (%)	14.2	17.2	13.1	14.1	13.2	13.4	13.9	13.6
HDW (%)	2.77	3.19*	2.91	2.49	1.96	2.04	1.94	1.69**
WBC (10^9/L)	4.2	4.5	4.4	4.0	3.6	4.2	3.5	3.6
Neut (10^9/L)	0.84	0.93	1.03	0.77	1.96	2.14	1.62	1.69
Leuc (10^9/L)	3.31	3.36	3.20	3.06	1.44	1.80	1.73	1.66
Mono (10^9/L)	0.07	0.09	0.09	0.09	0.12	0.15	0.13	0.17
Eos (10^9/L)	0.09	0.09	0.08	0.07	0.05	0.04	0.04	0.04
Baso (10^9/L)	0.00	0.01	0.00	0.00	0.00	0.01	0.00	0.00
Plt (10^9/L)	763	810	865	912**	1007	1025	1041	1156*
MPV (fL)	7.4	7.4	7.5	7.6	7.3	7.3	7.3	7.4
PDW (%)	55.0	52.9	54.8	51.4	49.6	47.9	50.2	48.0
PT (sec)	23.1	22.1	23.6	28.1***	22.9	23.0	23.3	23.3
APTS (sec)	17.2	17.3	17.4	17.7	16.2	16.2	16.4	17.3
Fib (g/L)	1.53	1.53	1.51	1.45	1.51	1.56	1.46	1.43

- *Clinical biochemistry findings :*

Table 4 : Biological clinical data

	Males (at post-pairing D 43)				Females (at LD 22)			
Dose level (in mg/kg bw/d)	0	20	50	100	0	20	50	100
AST (IU/L)	68	64	64	80	108	108	120	119
ALT (IU/L)	54	51	52	73*	69	70	78	80
ALP (IU/L)	70	67	63	74	74	69	71	62
Tot. chol. (mmol/L)	1.6	1.8	2.1*	2.0	1.8	1.4	1.7	1.9
Tot. prot. (µmol/L)	63	63	61	58***	57	55	56	55
A/G ratio	1.8	1.8	2.0*	2.2**	2.2	2.4	2.4	2.1
Urea (mmol/L)	8.6	8.9	9.4	9.2	11.8	12.0	12.7	11.3
Creat (µmol/L)	30	34	35**	34	28	30	30	28

- *Thyroid hormone :*

Table 5 : Thyroid hormone data

	Males (at post-pairing D 43)				Females (at LD 22)			
Dose level (in mg/kg bw/d)	0	20	50	100	0	20	50	100
IMT4 (nmol/l)	67	83	74	60	50	59	55	<50
TSHI (µlU/ml)	0.23	0.38	0.44	0.21	0.24	0.28	0.22	0.23

- *Effects on sperm :*

Table 6 : Sperm analysis

Dose level (in mg/kg bw/d)	0	20	50	100
Sperm count (epididymis) (Mio/g)	768.2	707.0	736.3	716.5
Sperm motility (%)	85	83	90	87
Average patch velocity (VAP) (µm/s)	124.3	120.2	131.3	134.7
Curvilinear velocity (VCL) (µm/s)	227.7	222.1	236.1	245.9
Straight line velocity (VSL) (µm/s)	87.1	84.6	91.6	94.5
Straightness (VSL/VAP)	67	67	69	70
Abnormal sperm (%)	11.2[A]	1.3	1.7	1.2

[A] : St. Dev. was of 31.23, while it was of 1.11, 1.48 and 1.38, resp. at 20, 50 and 100 mg/kg bw/d

- *Male fertility parameters :*

Table 7 : Male fertility parameters

Dose level (in mg/kg bw/d)	0	20	50	100
Males cohabitated	24	24	25	25
Males mating with at least 1 female	24	24	24	24
Males impregnating at least 1 female	23	22	24	23
Mating index (%)	100	100	96	96
Fecundity (%)	96	92	100	96
Fertility index (%)	96	92	96	92

- *Nb of females cycling normally and cycle length :*
  - *Nb of estrous cycles :* 2.2, 2.3, 2.2 and 2.0, resp. at 0, 20, 50 and 100 mg/kg bw/d.
  - *Mean cycle length :* 4.1, 4.1, 4.0 and 4.1 days, resp. at 0, 20, 50 and 100 mg/kg bw/d.
- *Fertility index :* 96, 92, 96 and 92 %, resp. at 0, 20, 50 and 100 mg/kg bw/d (nb of pregnant females : 24, 23, 24 and 23, resp. at 0, 20, 50 and 100 mg/kg bw/d (on 25 females mated per group)).
- *Duration of gestation (calculated from day 0 of pregnancy) :* 23.3, 23.3, 23.3 and 23.3 day, resp. at 0, 20, 50 and 100 mg/kg bw/d.
- *Nb of implantations, corpora lutea, litter size :*
  - *Mean nb of implantation sites :* 12.17, 11.74, 12.46 and 12.17, resp. at 0, 20, 50 and 100 mg/kg bw/d.
- *Nb of pre- and post-implantation loss :*
  - *% of post-implantation loss :* 0.54, 0.61, 1.29 and 1.09 %, resp. at 0, 20, 50 and 100 mg/kg bw/d.
- *Nb of dams with abortions, early deliveries, stillbirths, resorptions and/or dead fetuses :*
  - *Nb of females with liveborn pups :* 24, 23, 24 and 23, resp. at 0, 20, 50 and 100 mg/kg bw/d.
  - *Nb of females with stillborn pups :* 2, 3, 0 and 0, resp. at 0, 20, 50 and 100 mg/kg bw/d.
  - *Nb of females with no liveborn pups :* 0 in all groups.
- *Necropsy findings :* no treatment-related effect
- *Organ weight :*

Table 8 : Organ weight (in g or %)

		Males				Females			
Dose level (in mg/kg bw/d)		0	20	50	100	0	20	50	100
Nb examined		24	24	25	24	24	23	24	21
FBW		431.2	441.7	449.4	434.8	250.7	250.3	255.7	247.9
Adrenal	Abs	0.059	0.063	0.068*	0.066	0.083	0.084	0.086	0.073*
	Rela	0.014	0.014	0.015	0.015	0.033	0.034	0.034	0.030*
Brain	Abs	2.059	2.083	2.120	2.057	1.891	1.918	1.939	1.922

	Rela	0.481	0.475	0.475	0.476	0.757	0.768	0.760	0.777
Heart	Abs	1.068	1.049	1.075	1.069	0.941	0.882	0.905	0.906
	Rela	0.248	0.238	0.240	0.246	0.375	0.352	0.355	0.366
Kidneys	Abs	2.492	2.518	2.558	2.528	1.934	1.907	1.982	1.976
	Rela	0.579	0.570	0.571	0.582	0.772	0.762	0.777	0.797
Liver	Abs	10.861	11.177	11.261	10.398	9.689	9.755	9.880	9.958
	Rela	2.511	2.525	2.506	2.389	3.869	3.899	3.872	4.013
Pituitary	Abs	0.010	0.010	0.010	0.010	0.012	0.013	0.013	0.013
	Rela	0.002	0.002	0.002	0.002	0.005	0.005	0.005	0.005
Spleen	Abs	0.666	0.661	0.705	0.701	0.538	0.541	0.584	0.610*
	Rela	0.155	0.150	0.157	0.161	0.214	0.216	0.229	0.246**
Thymus	Abs	0.318	0.317	0.324	0.331	0.153	0.148	0.163	0.146
	Rela	0.074	0.072	0.072	0.077	0.061	0.059	0.064	0.059
Thyroid/parathyroid	Abs	0.020	0.020	0.020	0.020	0.015	0.016	0.016	0.016
	Rela	0.005	0.005	0.005	0.005	0.006	0.006	0.006	0.006
Epididymis	Abs	1.574	1.578	1.633	1.604	-	-	-	-
	Rela	0.367	0.361	0.365	0.370	-	-	-	-
Prostate	Abs	1.214	1.191	1.129	0.977***	-	-	-	-
	Rela	0.283	0.270	0.254	0.225***	-	-	-	-
Seminal vesicle	Abs	1.246	1.176	1.122	1.055	-	-	-	-
	Rela	0.292	0.270	0.250	0.242	-	-	-	-
Testis	Abs	3.579	3.659	3.734	3.682	-	-	-	-
	Rela	0.833	0.835	0.833	0.854	-	-	-	-
Ovary	Abs	-	-	-	-	0.085	0.084	0.087	0.086
	Rela	-	-	-	-	0.034	0.034	0.034	0.035
Uterus	Abs	-	-	-	-	0.517	0.530	0.635	0.629
	Rela	-	-	-	-	0.205	0.212	0.250	0.256

- *Histopathological findings :*

  Liver : higher incidence of centrilobular hepatocytes degeneration/regeneration in both sexes (more severe in males) and higher incidence of hepatocellular karyomegaly/multinucleation in females.

Table 9 : Incidence of centrilobular hepatocytes degeneration/regeneration

	Males				Females			
Dose level (in mg/kg bw/d)	0	20	50	100	0	20	50	100
Centrilobular hepatocytes degeneration/regeneration								
NP	24	13	1	0	24	20	12	10
Garde 1	0	11	18	10	0	3	12	11
Grade 2	0	0	6	11	0	0	0	0
Grade 3	0	0	0	3	0	0	0	0
Karyocytomegaly/multinucleation								
NP	24	24	25	24	24	24	23	17
Grade 1	0	0	0	0	1	1	2	6

Prostate : contraction was noted in 5 males at the highest dose and was characterized by lower secretions within the gland and an overall reduction in glandular size.

Spleen : increased splenic pigment was observed in all dose groups and in both sexes (characterized by yellow-brown, granular pigment within the splenic red pulp).

Table 10 : Incidence of splenic pigment

	Males				Females			
Dose level (in mg/kg bw/d)	0	20	50	100	0	20	50	100
Nb animal examined	24	24	25	24	24	23	24	21
Grade 1	6	11	6	5	9	11	8	1
Grade 2	3	10	16	14	2	12	15	14
Grade 3	-	-	2	5	-	-	1	6

For F1 pups/litters (per dose) :

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

Table 11 : Mean nb of live pups

Dose level (in mg/kg bw/d)	0	20	50	100
Tot nb of pups delivered	281	259	268	255
Mean nb of pups delivered	11.71	11.26	11.17	11.09
Mean nb of liveborn pups	11.63	11.13	11.17	11.09
Tot nb of stillborn pups	2	3	0	0
Livebirth index (%)	99	99	100	100

- *Sex ratio : mean percentage of males by litter :* 51, 47, 52 and 51 %, resp. at 0, 20, 50 and 100 mg/kg bw/d.
- *Viability index (pups surviving 4 days/total births) :* 99, 98, 98 and 92 %, resp. at 0, 20, 50 and 100 mg/kg bw/d.
- *Nb of dead pups :*
    - *Days 0-4 :* 3, 6, 2 and 11, resp. at 0, 20, 50 and 100 mg/kg bw/d (at the highest dose, 1 entire litter dead).
    - *Days 5-21 :* 4, 3, 0 and 1, resp. at 0, 20, 50 and 100 mg/kg bw/d.
- *Survival index at weaning :* 99, 99, 100 and 95 %, resp. at 0, 20, 50 and 100 mg/kg bw/d.
- *Mean litter or pup weight by sex and with sexes combined :*

Table 12 : Mean pup weight (in g)

	Males				Females			
Dose level (in mg/kg bw/d)	0	20	50	100	0	20	50	100
D 1	7.00	7.02	7.05	6.95	6.72	6.75	6.66	6.72
D 4	10.69	10.65	10.39	10.29	10.43	10.35	9.86	10.01
D 7	15.50	15.73	14.91	14.84	15.16	15.28	14.41	14.48
D 14	28.75	29.43	27.67	27.24	28.17	28.63	26.99	26.79
D 20	43.72	44.29	41.98	41.14	43.27	43.47	41.15	40.91

- *Ano-genital distance (at PND 4) :*
    - *In males :* 4.5, 4.6, 4.4 and 4.6 mm , resp. at 0, 20, 50 and 100 mg/kg bw/d.

- *In females :* 2.1, 2.1, 1.8 and 1.9 mm, resp. at 0, 20, 50 and 100 mg/kg bw/d.

- *Males nipples/areolae count at PND 13 :* 0 in all groups.
- *Thyroid hormones :*

Table 13 : Thyroid hormone data (At PND 22)

	Males				Females			
Dose level (in mg/kg bw/d)	0	20	50	100	0	20	50	100
IMT4 (nmol/l)	67	81	76	91**	69	73	70	73
TSHI (µIU/ml)	<0.09	<0.10	<0.09	<0.11	<0.09	0.11	<0.09	0.11

- *Macroscopic observation :* no treatment-related effects
- *Organ weight :*

Table 14 : Organ weight (in g or %)

		Males				Females			
Dose level (in mg/kg bw/d)		0	20	50	100	0	20	50	100
FBW		47.4	47.3	45.9	46.9	46.3	48.6	43.3	44.8
Brain	Abs	1.4038	1.2144	1.4270	1.4321	1.3840	1.3853	1.3845	1.3818
	Rela	2.9871	3.0123	3.1633	3.0969	0.0301	2.8967	3.2483	3.1259
Spleen	Abs	0.2131	0.2154	0.1893	0.1932	0.2161	0.2187	0.1851	0.1901
	Rela	0.4477	0.4516	0.4054	0.4109	0.4651	0.4464	0.4203	0.4226
Thymus	Abs	0.2136	0.2111	0.2052	0.1830*	0.2285	0.2337	0.2104	0.1938*
	Rela	0.4519	0.4460	0.4492	0.3935**	0.4940	0.4819	0.4873	0.4330**

- *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) :* no information available

For cohort 1A (per dose) :

- *Time of death during the study and whether animals survived to termination :*

  At 0 mg/kg bw/d : on male was found dead on PND 25.

  At 100 mg/kg bw/d : one female was sacrificed on PND 82 due to poor general condition (necropsy did not revealed findings).

- *Clinical observations :* increase salivation was observed in all tested groups.
- *Body weight data :*

Table 15 : Body weight data (in g)

	Males				Females			
Dose level (in mg/kg bw/d)	0	20	50	100	0	20	50	100
D 22	49.9	49.4	49.9	48.0	49.9	48.6	48.4	46.3
D 32	108.8	108.6	110.1	108.9	101.3	99.6	99.5	99.6
D 50	218.3	219.8	221.4	219.8	161.6	159.0	158.4	161.9
D 64	291.4	292.6	291.6	294.1	189.0	185.5	186.4	191.8
D 85	353.2	356.5	356.3	358.8	213.8	211.6	214.3	216.2

D 92	-	-	-	-	205.5	201.5	209.4	204.9

- *Balano-preputial separation :* 48, 48, 50 and 51 days, resp. at 0, 20, 50 and 100 mg/kg bw/d (mean bw at completion : 208.0, 207.1, 217.9 and 224.3 g, resp. at 0, 20, 50 and 100 mg/kg bw/d).
- *Vaginal opening :* 35, 36, 35 and 36 days, resp. at 0, 20, 50 and 100 mg/kg bw/d (mean bw at completion : 112.7, 114.5, 111.5 and 115.7 g, resp. at 0, 20, 50 and 100 mg/kg bw/d).
- *Haematological findings :*

Table 16 : Haematological data

	Males (at D 85/87)				Females (at D 85)			
Dose level (in mg/kg bw/d)	0	20	50	100	0	20	50	100
Hb (g/dL)	14.7	14.6	14.3	14.5	14.1	13.9	13.7	13.5
RBC (10^{12}/L)	8.18	8.18	8.08	7.78*	7.82	7.47	7.24**	6.82
PCV (%)	43.8	43.4	42.9	43.2	43.2	42.5	42.1	42.4
MCV (fL)	53.6	53.1	53.1	55.7*	55.4	57.0	58.2**	62.2***
MCH (pg)	18.0	17.8	17.6	18.6	18.0	18.6	18.9	19.8***
MCHC (g/dL)	33.6	33.6	33.2	33.4	32.6	32.7	32.5	31.9
Ret (%)	2.5	2.7	3.0**	3.2***	3.1	3.7*	3.6	4.0**
RDW (%)	12.8	14.2	12.7	14.9*	11.0	11.8	11.3	11.8
HDW (%)	2.76	3.07	2.93	2.84	1.97	2.07	1.95	1.77**
WBC (10^9/L)	4.3	5.4	5.3	4.8	1.8	2.8	2.8	2.9
Neut (10^9/L)	0.79	0.92	0.89	0.77	0.30	0.45	0.47*	0.37
Leuc (10^9/L)	3.33	4.25	4.18	3.79	1.46	2.25	2.24	2.41
Mono (10^9/L)	0.08	0.10	0.10	0.10	0.04	0.05	0.07	0.07
Eos (10^9/L)	0.07	0.11*	0.09	0.06	0.03	0.05	0.05	0.03
Baso (10^9/L)	0.00	0.01	0.01	0.01	0.00	0.00	0.00	0.00
Plt (10^9/L)	760	868**	876**	958***	777	848	893*	946**
MPV (fL)	6.7	6.9	7.2**	7.0	8.1	8.4	8.1	7.8
PDW (%)	49.7	50.8	49.3	50.4	56.7	55.9	54.0	50.9***
PT (sec)	21.3	20.9	21.7	23.8***	22.8	23.1	23.0	23.4
APTS (sec)	15.3	16.2	15.6	16.5	15.4	16.0	16.4	17.5**
Fib (g/L)	1.55	1.57	1.58	1.51	1.17	1.27	1.24	1.23

- *Clinical biochemistry :*

Table 17 : Clinical biochemistry data

	Males (at D 85/87)				Females (at D 85)			
Dose level (in mg/kg bw/d)	0	20	50	100	0	20	50	100
AST (IU/L)	71	73	79	90***	65	71	76	66
ALT (IU/L)	44	49	48	60*	38	48	41	39
ALP (IU/L)	107	97	91	86	57	51	51	47
Chol (mmol/L)	1.6	1.7	1.7	1.8	1.1	1.1	1.4	1.8***
Tot. prot.	61	61	61	58*	62	60	63	59
A/G ratio	1.8	1.8	1.9	2.0	2.4	2.4	2.3	2.5

- *Thyroid hormone :*

Table 18 : Thyroid hormone data

	Males (at D 85)				Females (at D 85)			
Dose level (in mg/kg bw/d)	0	20	50	100	0	20	50	100
IMT4 (nmol/L)	73	80	73	73	<31	47	<36	<33
TSHI (µlU/mL)	0.46	0.27	0.27*	0.28	0.17	0.20	0.13	0.14

- *Effects on sperm :*

Table 19 : Sperm parameters data

Dose level (in mg/kg bw/d)	0	20	50	100
Sperm count (epididymis) (Mio/g)	835.9	796.3	831.0	812.6
Sperm motility (%)	76	81	79	70
Average patch velocity (VAP) (µm/s)	124.0	135.4	135.2	132.6
Curvilinear velocity (VCL) (µm/s)	220.7	239.7	239.6	230.9
Straight line velocity (VSL) (µm/s)	85.4	93.2	96.7	94.2
Straightness (VSL/VAP)	65	68	70	70
Abnormal sperm (%)	0.7	0.6	0.8	1.3

- *Average follicle count :*

Table 20 : Average follicle count

Dose level (in mg/kg bw/d)	Primordial	Primary	Secondary	Tertiary	Total
0	17	3	1	0	21
100	19*	4	1	0	24*

- *Nb of females cycling normally and cycle length :*
  - *Nb of oestrous cycle :* 1.9, 2.1, 2.5 and 2.0, resp. at 0, 20, 50 and 100 mg/kg bw/d.
  - *Mean cycle length :* 4.1, 4.1, 4.1 and 4.5 days, resp. at 0, 20, 50 and 100 mg/kg bw/d.
- *Necropsy findings :* no treatment-related effect
- *Organ weight :*

Table 21 : Organ weight data (in g or %)

		Males				Females			
Dose level (in mg/kg bw/d)		0	20	50	100	0	20	50	100
FBW		346.8	348.0	346.2	349.2	207.1	203.5	207.2	208.2
Adrenal	Abs	0.067	0.070	0.072	0.071	0.072	0.071	0.072	0.069
	Rela	0.0194	0.0201	0.0208	0.0205	0.0350	0.0346	0.0349	0.0334
Brain	Abs	1.959	1.959	1.949	1.950	1.783	1.790	1.820	1.815
	Rela	0.5670	0.5652	0.5648	0.5634	0.8654	0.8837	0.8827	0.8743
Heart	Abs	0.966	0.966	0.959	0.997	0.697	0.673	0.678	0.718
	Rela	0.2791	0.2776	0.2777	0.2872	0.3372	0.3311	0.3270	0.3451
Kidneys	Abs	2.209	2.274	2.217	2.309	1.526	1.501	1.548	1.634*
	Rela	0.6382	0.6544	0.6412	0.6623	0.7375	0.7376	0.7463	0.7864*
Liver	Abs	10.051	10.207	10.120	10.334	5.601	5.719	6.182**	6.690***
	Rela	2.8913	2.9273	2.9175	2.9675	2.7104	2.8117	2.9774***	3.2163***
Pituitary	Abs	0.009	0.010	0.009	0.010	0.011	0.012	0.012	0.014**
	Rela	0.0027	0.0029	0.0027	0.0030	0.0054	0.0058	0.0060	0.0065

Spleen	Abs	0.634	0.626	0.638	0.653	0.449	0.433	0.443	0.467
	Rela	0.1822	0.1800	0.1847	0.1879	0.2175	0.2130	0.2140	0.2244
Thymus	Abs	0.474	0.493	0.524	0.527	0.394	0.373	0.376	0.403
	Rela	0.1364	0.1414	0.1514	0.1519	0.1894	0.1839	0.1824	0.1933
Thyroid/parathyroid	Abs	0.018	0.018	0.018	0.019	0.015	0.016	0.014	0.014
	Rela	0.0053	0.0051	0.0051	0.0056	0.0071	0.0077	0.0066	0.0068
Epididymis	Abs	1.281	1.299	1.347	1.285	-	-	-	-
	Rela	0.3704	0.3730	0.3888	0.3706	-	-	-	-
Prostate	Abs	0.802	0.827	0.781	0.775	-	-	-	-
	Rela	0.2314	0.2392	0.2253	0.2230	-	-	-	-
Seminal vesicle	Abs	0.964	0.890	0.810	0.764**	-	-	-	-
	Rela	0.2805	0.2576	0.2349	0.2209*	-	-	-	-
Testis	Abs	3.365	3.384	3.411	3.322	-	-	-	-
	Rela	0.9761	0.9761	0.9912	0.9557	-	-	-	-
Ovary	Abs	-	-	-	-	0.100	0.098	0.108	0.113
	Rela	-	-	-	-	0.0482	0.0482	0.0524	0.0543
Uterus	Abs	-	-	-	-	0.610	0.560	0.583	0.520
	Rela	-	-	-	-	0.2919	0.2768	0.2819	0.2511

- *Histopathological findings :*

  Liver : increased incidence of degeneration centrilobular of hepatocytes (minimal to slight) : 1, 16, 19 and 18 males and 0, 17, 17 and 17 females, resp. at 0, 20, 50 and 100 mg/kg bw/d (no higher incidence of necrosis, inflammatory cell foci or congestion/haemorrhage).

  Seminal vesicles : increased incidence of contraction (1, 2, 3 and 4 males, resp. at 0, 20, 50 and 100 mg/kg bw/d) and was characterized by decreased glandular secretions and an overall reduction in glandular size.

  Spleen : increased incidence of splenic pigment (characterized by yellow-brown, granular pigment within the splenic red pulp).

Table 22 : Incidence of splenic pigment

	Males				Females			
Dose level (in mg/kg bw/d)	0	20	50	100	0	20	50	100
Nb animal examined	20	20	20	19	20	20	20	19
Grade 1	2	8	6	7	8	8	6	1
Grade 2	-	-	-	1	3	12	11	14
Grade 3	-	-	-	-	-	-	2	4

- *Immunophenotyping :*

Table 23 : Immunophenotyping data

	Males				Females			
Dose level (in mg/kg bw/d)	0	20	50	100	0	20	50	100
Spleen CD3 abs (cells/mg)	95489	122316	125595	103882	100866	102712	116905	96593
Spleen CD3 % of lymphocytes	38.8	38.3	39.3	39.2	35.3	37.7	41.8	38.1
Spleen CD4 abs (cells/mg)	51104	70469	77509	60140	62129	64590	74453	59968
Spleen CD4 % of lymphocytes	19.2	21.7	24.6	22.3	21.7	24.0	26.4	23.6
Spleen CD8 abs (cells/mg)	40479	47896	44722	40888	36436	35995	40115	34901

Spleen CD8 % of lymphocytes	16.6	15.2	13.7	15.8	12.7	12.9	14.6	13.8
Spleen CD45RA abs (cells/mg)	114791	137541	146495	112989	128573	134717	118693	104316
Spleen CD45RA % of splenocytes	45.3	45.3	45.2	42.8	45.5	45.7	40.6	42.0
Spleen CD161A abs (cells/mg)	14143	17423	15567	9898	18399	15720	14952	11877
Spleen CD161+ % of splenocytes	6.8	5.4	5.1	4.1**	6.8	5.9	5.3	4.8

For cohort 1B (per dose) :

- *Clinical observations :* no treatment-related effects
- *Body weight data :*
  - *In males :*

Table 24 : Body weight in males (in g)

Dose level (in mg/kg bw/d)		0	20	50	100
Pre-pairing period	D 22	50.7	51.4	49.7	48.1
	D 30	95.6	97.6	109.9	109.8
	D 43	179.1	180.4	178.8	179.0
	D 64	292.4	297.8	295.4	295.4
	D 78	339.1	346.5	345.1	345.7
	D 92	372.9	382.6	379.5	380.0
Pairing period	D 1	376.2	385.1	383.3	384.6
	D 14	396.3	408.7	408.5	404.0
Post-pairing period	D 8	408.8	421.9	421.9	416.7

  - *In females :*

Table 25 : Body weight in females (in g)

Dose level (in mg/kg bw/d)		0	20	50	100
Pre-pairing period	D 22	50.0	49.7	48.3	47.2
	D 30	90.0	90.6	90.7	88.8
	D 43	141.5	144.3	146.3	142.0
	D 64	185.6	192.1	198.8	193.3
	D 78	204.8	213.1	219.5	212.2
	D 92	216.1	226.0	232.7	222.9
Gestation period	D 6	236.8	245.7	256.8*	250.5
	D 14	263.9	274.4	288.2*	278.3
	D 20	315.4	331.9	346.9*	334.5
Lactation period	D 1	250.5	258.6	274.1*	267.1
	D 4	258.4	268.4	278.3	278.3

- *Food consumption :* slightly increased at the highest dose in males and at the mid and high doses in females.
- *Haematological and clinical biochemistry findings :* not examined

- *Balano-preputial separation :* 49, 47, 50 and 51 PND, resp. at 0, 20, 50 and 100 mg/kg bw/d (bw at completion : 216.1, 207.2, 221.3 and 222.0 g, resp. at 0, 20, 50 and 100 mg/kg bw/d).
- *Vaginal opening :* 34, 36, 35 and 35 PND, resp. at 0, 20, 50 and 100 mg/kg bw/d (bw at completion : 110.4, 118.7, 113.1 and 110.6 g, resp. at 0, 20, 50 and 100 mg/kg bw/d).
- *Male fertility data :*

Table 26 : Male fertility data

Dose level (in mg/kg bw/d)	0	20	50	100
Males cohabitated	19	20	20	18
Males mating with at least 1 female	19	20	20	17
Mating index (%)	100	100	100	94
Fecundity index (%)	100	100	90	100
Fertility index (%)	100	100	90	94

- *Oestrous cycle :*
  - *Mean nb of oestrous cycle :* 2.7, 3.3, 3.1 and 2.4, resp. at 0, 20, 50 and 100 mg/kg bw/d.
  - *Mean cycle length :* 4.3, 4.2, 4.3 and 4.6 days, resp. at 0, 20, 50 and 100 mg/kg bw/d.
- *Female reproductive performance :* one pregnant female had no viable fetuses ([A]) and one pregnant female did not litter ([B]).

Table 27 : Female fertility data

Dose level (in mg/kg bw/d)	0	20	50	100
Nb of females cohabitated	19	20	20	19
Nb of pregnant females	19	20[A]	18	19[B]
Mating index (%)	100	100	100	95
Fecundity index (%)	100	100	90	100
Fertility index (%)	100	100	90	95

- *Duration of gestation :* 23.3, 23.4, 23.2 and 23.4 days, resp. at 0, 20, 50 and 100 mg/kg bw/d.
- *Effects on sperm :* not examined
- *Mean nb of implantation site s:* 12.26, 11.35, 12.28 and 9.79, resp. at 0, 20, 50 and 100 mg/kg bw/d .
- *Mean nb of post-implantation loss :* 1.94, 0.53, 1.28 and 0.33, resp. at 0, 20, 50 and 100 mg/kg bw/d.
- *Nb of dams with abortions, early deliveries, stillbirths, resorptions and/or dead fetuses :*
  - *Nb of females with liveborn pups :* 18, 19, 18 and 18, resp. at 0, 20, 50 and 100 mg/kg bw/d.
  - *Nb of females with stillborn pups :* 3, 3, 1 and 0, resp. at 0, 20, 50 and 100 mg/kg bw/d.
  - *Nb of females with no liveborn pups :* 0 in all dose groups.
- *Nb of live births :*
  - *Nb of pups delivered :* 187, 220, 199 and 179, resp. at 0, 20, 50 and 100 mg/kg bw/d.
  - *Mean nb of pups per dam :* 10.39, 11.58, 11.06 and 9.94, resp. at 0, 20, 50 and 100 mg/kg bw/d.
  - *Nb of stillborn pups :* 4, 4, 1 and 0, resp. at 0, 20, 50 and 100 mg/kg bw/d.

- *Necropsy findings :* no treatment-related effect
- *Organ weight :*

Table 28 : Organ weight (in g or %)

		Males				Females			
Dose level (in mg/kg bw/d)		0	20	50	100	0	20	50	100
FBW		410.6	422.3	422.8	416.2	258.1	267.7	280.6*	275.7
Pituitary	Abs	0.009	0.010	0.010	0.009	0.013	0.014	0.015	0.015
	Rela	0.002	0.002	0.002	0.002	0.005	0.005	0.005	0.005
Epididymis	Abs	1.384	1.396	1.436	1.346	-	-	-	-
	Rela	0.338	0.332	0.341	0.324	-	-	-	-
Prostate	Abs	1.053	1.075	1.069	0.972	-	-	-	-
	Rela	0.258	0.255	0.256	0.233	-	-	-	-
Seminal vesicle	Abs	1.070	1.109	1.076	0.834*	-	-	-	-
	Rela	0.261	0.261	0.255	0.202*	-	-	-	-
Testis	Abs	3.619	3.541	1.436	3.519	-	-	-	-
	Rela	0.884	0.843	0.341	0.846	-	-	-	-
Ovary	Abs	-	-	-	-	0.097	0.100	0.111*	0.110*
	Rela	-	-	-	-	0.038	0.038	0.039	0.040
Uterus	Abs	-	-	-	-	0.775	0.755	0.822	0.794
	Rela	-	-	-	-	0.302	0.283	0.294	0.289

- *Histopathological findings:* no treatment-related effects

For F2 pups/litters (per dose) :

- *Mean nb of live pups (litter size) :* 187, 220, 199 and 179, resp. at 0, 20, 50 and 100 mg/kg bw/d.
- *Live birth index :* 98, 98, 99 and 100 %, resp. at 0, 20, 50 and 100 mg/kg bw/d.
- *Sex ratio :* not mentioned
- *Viability index (pups surviving 4 days/total births) :* 100, 100, 99 and 95 %, resp. at 0, 20, 50 and 100 mg/kg bw/d.
- *Total pup culled at day 4 :* 181, 215, 195 and 171 pups, resp. at 0, 20, 50 and 100 mg/kg bw/d.

  2 dead pup at the highest dose.

  Pup missing : 1, 1, 3 and 6, resp. at 0, 20, 50 and 100 mg/kg bw/d.
- *Survival index at weaning :* /
- *Mean pup weight by sex :*

Table 29 : Mean pup body weight (in g)

	Males				Females			
Dose level (in mg/kg bw/d)	0	20	50	100	0	20	50	100
D 1	7.16	7.11	7.21	7.28	6.73	6.91	6.82	6.67
D 4	10.84	10.62	10.78	10.87	10.35	10.47	10.25	10.03

- *Mean ano-genital distance :*

- *In male :* 5.3, 5.0, 5.1 and 5.0 mm, resp. at 0, 20, 50 and 100 mg/kg bw/d.
- *In female :* 2.6, 2.5, 2.3 and 2.5 mm, resp. at 0, 20, 50 and 100 mg/kg bw/d.

- *Macroscopic observations :* no treatment-related effect

For cohort 2A (per dose) :

- *Time of death during the study and whether animals survived to termination :* no mortality occurred.
- *Clinical signs :* isolated instances of salivation (in few males of the mid and high doses and in few females of all treated groups).
- *Body weight data :*

Table 30 : Mean body weight (in g)

	Males				Females			
Dose level (in mg/kg bw/d)	0	20	50	100	0	20	50	100
D 22	52.5	50.8	51.4	47.9	51.0	49.0	49.5	45.0
D 32	111.7	110.9	113.1	108.4	101.7	98.9	99.5	96.7
D 43	180.5	182.4	183.3	177.8	143.8	142.0	142.0	141.8
D 57	264.3	266.1	274.0	266.6	178.5	173.5	178.0	176.9
D 64	289.4	300.5	309.3	301.9	190.7	187.2	188.7	189.9
D 71	310.8	324.8	335.9	326.6	199.4	197.4	201.9	199.6

- *Food consumption :* no treatment-related effect.
- *Balano-preputial separation :* 48, 48, 49 and 50 day at complete development, resp. at 0, 20, 50 and 100 mg/kg bw/d (bw at completion : 211.5, 213.5, 217.3 and 219.6 g, resp. at 0, 20, 50 and 100 mg/kg bw/d).
- *Vaginal opening :* 34, 32*, 33 and 34 day at complete development, resp. at 0, 20, 50 and 100 mg/kg bw/d (bw at completion : 109.3, 96.9, 104.0 and 106.3 g, resp. at 0, 20, 50 and 100 mg/kg bw/d).
- *Acoustic startle :*

Table 31 : Basic habituation data : mean maximum amplitude (Ne)

	Males				Females			
Dose level (in mg/kg bw/d)	0	20	50	100	0	20	50	100
Block 1	0.574	0.567	0.609	0.453	0.832	0.673	0.619	0.544
Block 2	0.677	0.587	0.653	0.540	0.715	0.709	0.828	0.528
Block 3	0.613	0.567	0.662	0.458	0.736	0.678	0.628	0.485
Block 4	0.613	0.599	0.606	0.505	0.657	0.602	0.591	0.529
Block 5	0.592	0.518	0.601	0.462	0.608	0.655	0.492	0.518

Table 32 : Prepulse inhibition data (in %)

	Males				Females			
Dose level (in mg/kg bw/d)	0	20	50	100	0	20	50	100
Db level : 74	2	1	-11	-3	-2	-0	-1	-1
Db level : 78	11	12	5	16	21	-10	20	12

Db level : 86	50	53	49	55	54	41	57	44

- *Locomotor activity (at day 64/66-69) :*
  - *Total activity :*

Table 33 : Total activity data

	Males				Females			
Dose level (in mg/kg bw/d)	0	20	50	100	0	20	50	100
0-5 min	339	340	373	350	294	281	289	285
5-10 min	311	308	341	314	254	247	222	221
10-15 min	284	259	313	279	243	222	231	223
15-20 min	298	303	304	274	230	195	212	226
20-25 min	290	265	279	274	233	217	217	182
25-30 min	267	289	282	284	201	193	205	172
Total (0-30 min)	1789	1764	1892	1775	1455	1356	1377	1311

  - *Total mobile count :*

Table 34 : Total mobile count data

	Males				Females			
Dose level (in mg/kg bw/d)	0	20	50	100	0	20	50	100
0-5 min	118	110	140	111	128	125	132	119
5-10 min	90	87	109	84	89	97	83	66
10-15 min	70	48	87	63	82	72	84	65
15-20 min	69	76	83	70	78	61	65	70
20-25 min	57	64	74	60	62	56	62	40
25-30 min	55	66	59	65	58	55	67	38
Total (0-30 min)	459	449	552	452	496	466	494	399

  - *Total rearing :*

Table 35 : Total rearing data

	Males				Females			
Dose level (in mg/kg bw/d)	0	20	50	100	0	20	50	100
0-5 min	40	43	46	35	77	65	79	65
5-10 min	29	28	28	23	48	49	53	38
10-15 min	26	22	27	21	42	37	52	38
15-20 min	19	24	23	23	45	32	42	33
20-25 min	18	22	20	18	31	31	39	26
25-30 min	17	25	15	14	31	36	43	16
Total (0-30 min)	149	162	159	133	274	249	308	215

- *Functional observational battery :*

Table 36 : FOB (at D 65/67-70 in males and 66/68-70 in females)

	Males				Females			
Dose level (in mg/kg bw/d)	0	20	50	100	0	20	50	100

Latency (sec)	3	3	2	2	0	1	1	2
Nb of fecal boli	0.3	0	0	0	0	0	0	0
Nb of rears	11	10	11	10	15	11	13	12
Nb of urine pools	1	1	1	1	0	0	0	0
Forelimb grip strength (kg)	0.826	0.902	0.868	0.734	0.478	0.461	0.546	0.538
Hindlimb grip strength (kg)	0.300	0.263	0.279	0.249	0.367	0.361	0.336	0.296
Average of respective test scores (mm)	62	68	76	66	70	73	75	82

- *Haematological and clinical biochemistry findings :* not examined
- *Necropsy findings :* no treatment-related effects observed
- *Organ weight :*

Table 37 : FBW and brain weight (in g or %)

		Males				Females			
Dose level (in mg/kg bw/d)		0	20	50	100	0	20	50	100
FBW		325.1	342.6	353.3	341.5	208.1	203.2	208.0	206.3
Brain	Abs	1.925	1.945	1.976	1.916	1.738	1.837*	1.818*	1.776
	Rela	0.5969	0.5702	0.5610	0.5641	0.8425	0.9107	0.8772	0.8692

- *Histomorphometry :* some statistically sign. changes observed (at PND 76)

Table 38 : Brain histomorphometry (measurement in microns)

	Male		Female	
Dose level (in mg/kg bw/d)	0	100	0	100
Measurement ID				
1A	1913	1815	1862	1882
1B	1810	1746	1840	1862
2A	1770	1650	1767	1588**
2B	1780	1630*	1676	1602
3A	3508	3445	3540	3454
3B	3525	3593	3497	3504
4A	344	320	344	296*
4B	353	320	347	297*
5A	613	607	601	581
5B	611	585	569	564
6A	590	589	626	610
6B	591	612	608	620
7A	1507	1547	1602	1551
7B	1537	1545	1558	1574
16	5620	5182	5305	5267
18	2792	2689	2627	2688

- *Histopathological findings :* no treatment-related effects

For cohort 2B (per dose) :

- *Time of death during the study and whether animals survived to termination :* no mortality occurred.
- *Clinical observations:* no treatment-related effect.
- *Body weight data (D 22) :* 49.0, 47.8, 48.6 and 46.7 g in M and 49.1, 49.9, 47.7 and 45.5 g in F, resp. at 0, 20, 50 and 100 mg/kg bw/d.
- *Haematological and clinical biochemistry findings :* not examined
- *Necropsy findings :* no treatment-related effects
- *Organ weight :*

Table 39 : FBW and brain weight (in g or %)

		Males				Females			
Dose level (in mg/kg bw/d)		0	20	50	100	0	20	50	100
FBW		49.1	47.9	48.8	46.8	49.1	49.5	47.3	45.4
Brain	Abs	1.414	1.410	1.427	1.405	1.400	1.382	1.384	1.391
	Rela	2.9136	2.9530	2.9459	3.0334	2.8720	2.8247	2.9581	3.0956

- *Histomorphometry:* some statistically sign. changes observed (at PND 22)

Table 40 : Brain morphometry (measurement in microns)

	Males		Females	
Dose level (in mg/kg bw/d)	0	100	0	100
Measurement ID				
1A	2046	2100	2129	2228
1B	2052	2022	2136	2254*
2A	1904	1774**	1876	2022*
2B	1902	1870	1964	1988
3A	3198	3194	3220	3324
3B	3296	3236	3264	3348
4A	229	226	230	233
4B	243	227	241	236
5A	563	573	628	652
5B	554	564	610	648
6A	519	536	591	618
6B	524	549	582	631*
7A	1403	1462	1560	1674
7B	1387	1491*	1539	1654*
16	5496	5512	5524	5432
18	2592	2536	2524	2604**

- *Histopathological findings:* no treatment-related effects

For cohort 3 (per dose):

- *Time of death during the study and whether animals survived to termination:* no mortality occured
- *Clinical observations:* a slight increase incidence of excessive salivation was observed

- *Body weight data:*

Table 41 : Body weight (in g)

	Males				Females			
Dose level (in mg/kg bw/d)	0	20	50	100	0	20	50	100
D 22	49.4	48.6	50.4	45.7	49.9	49.2	48.6	44.7
D 32	108.8	108.1	113.4	107.0	99.3	98.6	99.9	97.8
D 43	176.8	178.1	188.0	176.7	140.5	141.7	143.8	141.0
D 57	259.7	260.5	273.1	265.7	177.5	177.4	182.7	181.5
D 78	338.4	341.3	354.5	350.2	205.6	209.4	214.9	212.4

- *Food consumption :* no treatment-related effect.
- *Balano-preputial separation :* 50, 48, 49 and 49 days, resp. at 0, 20, 50 and 100 mg/kg bw/d (bw at completion : 215.6, 208.2, 220.4 and 218.7 g, resp. at 0, 20, 50 and 100 mg/kg bw/d).
- *Vaginal opening :* 32, 33, 34 and 36** days, resp. at 0, 20, 50 and 100 mg/kg bw/d (bw at completion : 99.0, 101.1, 107.2 and 115.1* g, resp. at 0, 20, 50 and 100 mg/kg bw/d).
- *Anti-KLH IgM and IgG cut point titre assay :*

Table 42 : Anti-KLH IgM and IgG

	Males				Females			
Dose level (in mg/kg bw/d)	0	20	50	100	0	20	50	100
KLHM (anti-KLH IgM cut point titre assay)								
D 59-65	858	819	1206	1029	2253	1476	609	1348
D 68-72	312	768	1168	483	870	718	403	327
D 76-78	9694	5880	9362	8254	10473	8314	7420	7517
D 84/85/87	1810	2368	4194	3051	2950	3112	2248	1932
KLHG (anti-KLH IgG cut point titre assay)								
D 59-65	399	676	958	844	840	1446	539	636
D 68-72	1344	4116	13132	3243	2983	4720	1831	2128
D 76-78	71891	97064	>153539	>165577	>187401	>120527	>119645	>96014
D 84/85/87	73625	83423	>120260	127560	>239000	>120451	>107761	>90902

- *Haematological and clinical biochemistry findings :* not examined
- *Necropsy findings :* no treatment-related effect
- *Organ weight :*

Table 43 : FBW and spleen weight (in g or %)

		Males				Females			
Dose level (in mg/kg bw/d)		0	20	50	100	0	20	50	100
FBW		351.5	352.1	367.0	362.9	209.5	210.9	222.6	219.6
Spleen	Abs	0.651	0.616	0.735	0.707	0.447	0.436	0.498	0.510
	Rela	0.1866	0.1757	0.2001	0.1964	0.2134	0.2068	0.2241	0.2324

3.10.1.2 Combined repeated dose toxicity with the reproduction/developmental toxicity screening test (Anonymous, 2012)

Study reference

Anonymous, 2012

Detailed study summary and results

Test type

OECD TG 422

GLP

Test substance

- 3,5-dimethylpyrazole
- *Degree of purity :* unspecified

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 :* approx. 11 weeks old, 287-326 g for M and 187-218 g for F

Administration/exposure

- *Route of administration :* oral, gavage
- *Duration and frequency of test/exposure period :* daily
    - *In males :* 29 to 31 days (2 weeks prior mating, during mating and up to the day prior to scheduled necropsy).
    - *In females :* 45 to 56 days (2 weeks prior mating, during pairing, gestation and up to lactation day 4).
- *Doses/concentration levels :* 0, 20, 60 and 200 mg/kg bw/d
- *Vehicle :* propylene glycol

Results and discussion

For P :

- *Time of death during the study and whether animals survived to termination :* 1 female of the highest dose was euthanized due to total litter loss.
- *Clinical observations :* no treatment-related effect.
- *Body weight data :*
    - *In males :* bw and bwg significantly lower at 200 mg/kg bw/d on PMD 8 and through the entire mating period.
    - *In females :* bwg sign lower at 200 mg/kg bw/d on PMD 8 and on PCD 11 and bwg was slightly reduced on PCD 7, 14-17 and 20.
- *Food consumption :* Absolute food consumption was lower for males at 200 mg/kg from Days 1-8 of the premating period while relative food consumption was lower during the entire premating period.

For females, relative food consumption was slightly lower during Days 1-8 of the premating period, and Days 17-20 of the post coitum period. Absolute and relative food consumption were both significantly lower than controls from lactation Days 1-4.

- *Water consumption :* at 200 mg/kg bw/d : increase in both sexes (in males, during the entire treatment period while in females, during the entire premating and post-coitum periods).

  At 60 mg/kg bw/d : higher in females over several days during the post-coitum period (never statistically sign.. The registration dossier mentions that a relationship to treatment could not be excluded).

- *Haematological and clinical biochemistry findings :* not examined
- *Sperm examination :* oligospermia, seminiferous cell debris and degeneration/depletion of spermatocytes were observed at the highest dose.
- *Nb of females cycling normally and cycle length :* not examined
- *Fertility index :* decrease at the highest dose (60 % vs 80 % in control group)

Table 44 : Female reproductive parameters

Dose level (in mg/kg bw/d)	0	20	60	200
Nb of female paired	10	10	10	10
Nb of females mated	10	10	10	9
Nb of females non-mated	0	0	0	1
Nb of pregnant females	8	9	9	6
Nb of non-pregnant females	2	2	1	3

- *Duration of gestation (calculated from day 0 of pregnancy) :* no information available
- *Precoital interval (nb of days until mating and nb of estrous periods until mating) :* unaffected (no more information available)
- *Nb of corpora lutea :* unaffected (no more information available)
- *Nb of implantations :* unaffected (no more information available)
- *Nb of pre- and post-implantation loss :* no information available
- *Data on functional observations :* not examined
- *Necropsy findings :*

  At 200 mg/kg bw/d : in males : reduced size of epididymides, testes and seminal vesicles in one male.

  In females : enlarged spleen and reduced size of the thymus were seen for 6/10 and 5/10 animals, resp.

- *Organ weight :*

  At 200 mg/kg bw/d : in males : lower FBW, testes (abs and rela), seminal vesicles (abs and rela), prostate (abs), epididymides (abs) and higher spleen (abs and rela), thyroids (rela) and kidney (rela) weights.

  In females : lower thymus (abs and rela) and higher spleen (abs and rela) weights.

At 20 and 60 mg/kg bw/d : higher spleen (abs and rela) weight.

No more information available

- *Histopathological findings :*

  Thymus : increased severity of lymphoid atrophy at the highest dose in 3 males out of 5 and in 5 females out of 5.

  Liver : hepatocellular basophilia (up to slight) and/or apoptosis/single cell necrosis (up to marked) in the area directly around the central veins in males exposed to 60 mg/kg bw/d and in both sexes exposed to 200 mg/kg bw/d. Furthermore, males of the highest dose exhibited hepatocellular karyomegaly (5 out of 5 males) and midzonal hepatocellular vacuolation (3 males out of 5).

  Spleen : higher severity of hematopoietic foci in males of the highest dose (6 out of 6, up to marked).

  Epididymides : 200 mg/kg bw/d: oligospermia (1 males out of 6, marked) + an increased incidence and/or severity of seminiferous cell debris (3 males out of 6, up to slight).

  Testes : 200 mg/kg bw/d: degeneration/depletion of spermatocytes (6 males out of 6, up to massive) + and increase incidence and/or severity of spermatic giant cells (5 males out of 6, up to moderate).

For pups/litters (per dose) :

- *Mean nb of live pups (litter size) :* no information available
- *Sex ratio :* no information available
- *Mortality (found dead or went missing) :* severely increased at the highest dose during the first days of lactation (3, 3, 1 and 13 pups, resp. at 0, 20, 60 and 200 mg/kg bw/d). 7 out of 13 dead pups at 200 mg/kg bw/d were attributable to one female who had a total litter loss by day 3.
- *Clinical signs :* lean, pale appearance, a wound or scab on the flank, swelling on the neck or abdomen, blue discoloration, cold, swelling of the abdomen, no milk in the stomach, blue hind legs or lumbar region and blue spot on the neck were observed. (no more information available)
- *Body weight :* sign. lower at the highest dose on LD 4, no other effects on pup body weights. (no more information available)
- *Viability index (pups surviving 4 days/total births) :* no information available
- *Survival index at weaning :* /
- *Gross pathology :*

  At 60 mg/kg bw/d : a single pup had small lower jaw

  Pups that were found dead exhibited incidental findings such as autolysis, absence of milk in the stomach, partial cannibalism (abdominal organs missing) and/or autolysis.

  Surviving pups had only scab on the left flank.

No more information available

3.10.1.3 Prenatal developmental study (Anonymous, 2018)

Study reference

Anonymous, 2018

Detailed study summary and results

Test type

OECD TG 414

GLP

Test substance

- 3,5-dimethylpyrazole
- *Degree of purity :* 99.98 %

Test animals

- *Species/strain/sex :* Rat / Wistar / female
- *Nb. of animals per sex per dose :* 22 timed-mated females/group
- *Age and weight at the study initiation :* 8 to 10 weeks (at the time of mating) and 180.2 to 267.1 g at the start of dosing.

Administration/exposure

- *Route of administration :* oral, gavage
- *Duration and frequency of test/exposure period :* GD 6 to 20, daily (females were maintained to GD 21, sacrificed and uterine contents were examined).
- *Doses/concentration levels, rationale for dose level selection :* 0, 20, 60 and 200 mg/kg bw/d
- *Vehicle :* propylene glycol

Results and discussion

For P (per dose) :

- *Time of death during the study and whether animals survived to termination :* no mortality occured
- *Clinical observations :* no treatment-related effect as thinning fur, minimal lesions, fur staining and pale teeth were observed in control and treated groups.
- *Body weight data :*

Table 45 : Body weight (in g)

Dose level (in mg/kg bw/d)	0	20	50	200
GD 3	207.5	211.1	208.4	208.2
GD 6	220.2	222.9	218.7	221.5
GD 15	258.4	256.0	253.4	243.5
GD 21	322.5	314.2	314.4	302.4
BWG GD 6-21	102.3	91.3	95.6	80.9***

- *Food consumption :* sign. reduced at the highest dose.
- *Haematological and clinical biochemistry findings :* not examined
- *Duration of gestation (calculated from day 0 of pregnancy) :* /
- *Nb of implantations, corpora lutea :*
    - *Mean nb of corpora lutea :* 12 in all groups.
    - *Mean nb of implantation sites :* 11, 10, 10 and 11, resp. at 0, 20, 60 and 200 mg/kg bw/d.
- *% of pre-implantation loss :* 11.4, 15.5, 10.5 and 5.7 %, , resp. at 0, 20, 60 and 200 mg/kg bw/d.
- *% of post-implantation loss :* 3.6, 8.9, 6.0 and 10.7 %, resp. at 0, 20, 60 and 200 mg/kg bw/d.
- *Nb of resorption :*
    - *Early :* 0, 1, 1 and 1, resp. at 0, 20, 60 and 200 mg/kg bw/d.
    - *Late :* 0 in all dose groups.
- *Nb of dams with abortions, early deliveries, stillbirths, resorptions and/or dead fetuses :*

Table 46 : Nb of pregnant females

Dose level (in mg/kg bw/d)	0	20	60	200
Nb of pregnant females	22	21	22	21
Nb of non-pregnant females	0	1	0	0
Nb of females with no viable fetuses	0	0	0	1

- *Mean nb of live births :* 11, 9, 10 and 10, resp. at 0, 20, 60 and 200 mg/kg bw/d.
- *Necropsy findings :* no treatment-related effects observed.
- *Body weight change and gravid uterine weight, including optionally, body weight change corrected for gravid uterine weight :*

Table 47 : Body weight change and uterus weight (in g)

Dose level (in mg/kg bw/d)	0	20	60	200
Gravid uterine weight	72.0	63.1	67.3	65.2
Corrected bw (carcass weight)	246.7	247.5	243.7	235.9
Corrected weight change D 3-21	39.2	36.3	35.3	27.7
Tot. weight change D 3-21	111.2	99.4	102.6	92.9

For F1 pups/litters (per dose) :

- *Tot. nb of litters :* 22, 21, 22 and 21, resp. at 0, 20, 60 and 200 mg/kg bw/d.
- *Tot. nb of fetuses :* 231, 194, 215 and 216, resp. at 0, 20, 60 and 200 mg/kg bw/d.
- *Mean nb of live pups (litter size) :* 11, 9, 10 and 10, resp. at 0, 20, 60 and 200 mg/kg bw/d.
    - *Mean nb of male fetuses per litter :* 6, 5, 5 and 5, resp. at 0, 20, 60 and 200 mg/kg bw/d.
    - *Mean nb of female fetuses per litter :* 5, 4, 5 and 5, resp. at 0, 20, 60 and 200 mg/kg bw/d.
- *Sex ratio :* 54, 50, 49 and 43 % of males, resp. at 0, 20, 60 and 200 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 48 : Mean fetal weight (in g)

Dose level (in mg/kg bw/d)	0	20	60	200
Mean fetal weight	5.17	5.12	5.18	4.62
Mean male fetuses weight	5.27	5.31	5.35	4.74
Mean female fetuses weight	4.99	4.89	5.02	4.53

- *External, soft tissue and skeletal malformations and other relevant alterations :*
  - *Malformation :* 16 fetuses from 9 litters exhibited malformations compared to 4 fetuses from 4 litters in control group).

    Supernumerary digit/polydactyly : in 3 fetuses from 2 litters of the highest dose.

    Bent scalula blade : in 1 fetus at the low dose and in 6 fetuses from 3 litters at the highest dose.

    Diaphragmatic cyst and short humerus were noted at 200 mg/kg bw/d.
  - *Variation :*

Table 49 : Incidence of variation

Dose level (in mg/kg bw/d)			0	20	60	200	HCD
Blood vessel	Umbilical artery – left sided	% litter	41	43	45	86**	59.34
		% fetal	8.54	9.41	10.74	29.27	17.09
Skull	Presphenoid – incomplete ossification	% litter	5	15	0	24	NP
		% fetal	0.79	3.00	0.00	6.63	
	Suture – sutural bone	% litter	5	5	0	33*	NP
		% fetal	0.68	1.67	0.00	7.30	
Pelvic gridle	Iliac alignment – abnormal	% litter	19	20	18	95***	15
		% fetal	3.62	3.83	5.91	89.59	5
Sternebra	Additional ossification site	% litter	0	0	0	24*	0.82
		% fetal	0.00	0.00	0.00	7.30	0.15
	Incomplete ossification	% litter	0	10	5	38**	14.50
		% fetal	0.00	1.83	1.82	18.87	3.43
Vertebra	Cervical centrum – incomplete ossification	% litter	43	55	36	81*	37.50
		% fetal	10.60	18.08	12.66	30.71	10.67
	Cervical centrum - unossified	% litter	67	80	45	86	30
		% fetal	26.29	37.17	19.70	59.16	9.59
	Thoracic centrum – incomplete ossification	% litter	19	5	14	48	27.50
		% fetal	4.85	0.83	2.47	12.32	6.11
Hindlimb	Metatarsal – incomplete ossification	% litter	5	10	14	33*	17.50
		% fetal	0.95	3.00	2.69	8.15	4.02
	Metatarsal - unossified	% litter	19	30	32	43	2.50
		% fetal	3.89	8.33	11.82	16.43	0.63

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 Combined repeated dose toxicity with the reproduction/developmental toxicity screening test (Anonymous, 2012)

See section 3.10.1.2

3.12.1.2 Extended One-Generation reproductive toxicity study (Anonymous, 2020)

See section 3.10.1.1

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

Hazard class not assessed in this dossier

5 REFERENCES

Dewitt J.B. *et al.*, 1953, Relationship between chemical structure and toxic action on rats, Chemical biological coordination centre, review no. 5 national research council, Washington D.C.

Full study reports

Registration dossier : https://echa.europa.eu/fr/registration-dossier/-/registered-dossier/5791/1/1

6 ABBREVIATIONS

* : $p < 0.05$

** : $p < 0.01$

*** : $p < 0.001$

A/G : albumin/globuline ratio

Abs : absolute

AGD : ano-genital distance

ALP : alkaline phosphatase

ALT : alanine aminotransferase

Approx. : approximately

APTS : activated partial thromboplastin time

AST : aspartate aminotransferase

Baso : basophils

Bw : body weight

Bwg : body weight gain

Chol. : cholesterol

Creat : creatinine (enzymatic)

Eos : eosinophils

F : female

FBW : final body weight

Fib : fibrinogen

FOB : functional observational battery

GD : gestation day

GLP : good laboratory practise

Hb : haemoglobin

HCD : historical control data

HDW : haemoglobin distribution width

Ig : immunoglobulin

IMT4 : imulite total T4

KLH : keyhole limpet hemocyanin

LC_{50} : lethal concentration 50%

LD : lactation day

LD_0 : lethal dose 0%

LD_{50} : lethal dose 50%

Leuc : leucocyte

Lymph : lymphocytes

M : male

MCH : mean cell haemoglobin

MCHC : mean cell haemoglobin concentration

MCV : mean cell volume

Mono : monocytes

MPV : mean platelet volume

Nb : number

Neut : neutrophils

NP : not present

PCD : post-coital day

PCV : packed cell volume

PDW : platelet distribution width

Plt : platelets

PMD : post-mating day

PND : post-natal day

PT : prothrombine time

RBC : red blood cells

RDW : red cell distribution width

Rela : relative

Resp. : respectively

Ret : reticulocytes

SD : Sprague Dawley

Sign. : significant(-ly)

St. Dev. : standard deviation

TG : test guideline

Tot. : total

Tot. chol. : total cholesterol

Tot. prot. : total protein

TSHI : rapid thyroid stimulating hormone

VAP : average patch velocity

VCL : curvilinear velocity

VSL : straight line velocity

WBC : white blood cell