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:

4,4'-sulphonyldiphenol; bisphenol S

EC Number: 201-250-5

CAS Number: 80-09-1

Index Number: NA

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Not evaluated in this dossier

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Study reference:

Anonymous 12, 2000

Detailed study summary and results:

Test type

According to OECD TG 421

GLP

Test substance

- 4,4'-sulphonyldiphenol
- *Degree of purity :* see confidential annex

Test animals

- *Species/strain/sex :* rat / SD / male + female
- *No. of animals per sex per dose :* 12/sex/dose
- *Age and weight at the study initiation :* 9 w old

  329 – 374 g in males and 206 – 251 g in females

Administration/exposure

- *Route of administration :* gavage
- *duration of test/exposure period :*
  - males : a total of 45 days (14 d of pre-mating period, through mating period to the day before necropsy)
  - females : a total of 40 to 46 days (14 d before mating, mating through gestation and until LD 3) (females without delivery were exposed until D 25 after confirmation of copulation)
- *frequency of exposure :* daily
- *doses/concentration levels :* 0, 10, 60 and 300 mg/kg bw/d
- *vehicle :* 0.5 % aqueous sodium CMC solution with 0.1 % Tween 80

Results and discussion

For P adults :

- *clinical observations :* 300 mg/kg bw/d : excessive salivation was noted immediately before or immediately after administration in 7 males and 1 female. However, all of them recovered ± 30 min after administration.

- *body weight data for P animals selected for mating :* a lower bwg was observed at the highest dose in both sexes. Moreover, a significantly decrease bw was noted in females at day 4 of lactation was observed at the mid dose level.

Table 1 : body weight data (g)

Dose level (mg/kg bw/d)			0	10	60	300
Males		Nb of animals examined	12	12	12	12
		D 0	351.9	354.3	352.5	354.2
		D 3	373.8	373.5	373.7	357.5*
		D 14	435.9	435.9	437.9	404.5**
		D 42	511.8	514.5	523.5	486.0
		BWG D 0-42	159.9	160.2	171.0	131.8
Females	Premating	Nb of animals examined	12	12	12	12
		D 0	229.1	228.4	228.2	230.3
		D 14	264.2	263.8	262.3	251.7
		BWG D 0-14	35.1	35.4	34.1	21.4**
	Gestation	Nb of animals examined	11	11	12	7
		D 0	272.8	277.1	266.8	264.4
		D 20	436.5	433.1	418.6	390.4**
		BWG D 0-20	163.6	156.0	151.8	126.0**
	Lactation	Nb of animals examined	11	11	12	7
		D 0	325.5	327.5	314.3	316.0
		D 4	360.1	354.1	333.0*	338.6
		BWG D 0-4	34.5	26.5	18.7	22.6

* : $p < 0.05$; ** : $p < 0.01$

- *precoital interval (number of days until mating and number of oestrus periods until mating) and reproductive performance :* extended cycles were noted at the highest dose. Five females showed a dioestrus period of 6 to 10 days and 4 out of these 5 females did not conceive.

Table 2 : reproductive performance

Dose level (mg/kg bw/d)	0	10	60	300
Mean duration of oestrus cycle in days	4.08	4.01	4.14	5.57**
Incidence of females with irregular oestrus cycle	0/12	0/12	1/12	5/12*
Copulation index in %	100.00	100.00	100.00	100.00
Fertility index in % (nb. of pregnant females/nb. of copulated females)	91.7 (11/12)	91.7 (11/12)	100.00 (12/12)	58.3 (7/12)

* : $p < 0.05$; ** : $p < 0.01$

- *number of implantations, corpora lutea, litter size :* a significant decrease in the implantation index was observed at the highest dose. Furthermore, a lower total number of offspring was observed at this dose level.

Table 3 : delivery data

Dose level (mg/kg bw/d)	0	10	60	300
Nb of animals examined	11	11	12	7
Gestation length (d)	22.9	23.0	22.8	22.9
Mean nb of corpora lutea	16.6	15.9	17.3	15.7
Mean nb of implantation sites	15.9	13.3	14.8	10.7
Mean nb of offspring	14.3	12.5	13.5	9.1
Implantation index (%)	95.80	80.84	86.15	64.89**
Delivery index (%)	90.03	94.60	91.22	89.57
Gestation index (%)	100.00	100.00	100.00	100.00

** : $p < 0.01$

- *effect on sperm :* not examined
- *necropsy findings :* distension of the cecum was noted in 1 male and 1 female at 60 mg/kg bw/d and in all males (12) and 4 females at 300 mg/kg bw/d
- *body weight at sacrifice and absolute and relative organ weight data for the parental animals :* changes in organ weights were observed at 300 mg/kg bw/d (see table 4)

Table 4 : organ weight

	Males				Females			
Dose level (mg/kg bw/d)	0	10	60	300	0	10	60	300
FBW (g)	513.4	517.3	526.7	488.1	360.1	354.1	333.0*	338.6
Liver (g)	16.373	16.246	16.803	17.439	15.289	14.114	14.490	14.393
Liver rel.	3.185	3.135	3.185	3.562**	4.247	3.989	4.359	4.246
Pituitary (mg)	14.92	13.60	15.12	16.68	21.18	21.64	21.45	21.07
Pituitary rel. ($x10^{-3}$)	2.89	2.63	2.88	3.43**	5.90	6.14	6.45	6.21
Thymus (mg)	289.6	336.3	332.1	254.5	263.1	312.7	253.5	221.7
Epididymis (g)	1.355	1.292	1.328	1.292	-	-	-	-
Prostate (g)	0.723	0.746	0.777	0.708	-	-	-	-
Sem. ves. (g)	2.825	2.718	2.860	2.428**	-	-	-	-
Sem. ves. rel.	0.552	0.531	0.546	0.498	-	-	-	-
Testes (g)	3.559	3.480	3.554	3.503	-	-	-	-
Ovaries (mg)	-	-	-	-	110.35	116.02	114.86	105.63
Uterus (g)	-	-	-	-	0.691	0.683	0.713	0.700

* : $p < 0.05$; ** : $p < 0.01$

- *histopathological findings:* changes observed in cecum and liver at both sexes (see table 5)

Table 5 : incidence of histopathological findings

		Males				Females			
Dose level (mg/kg bw/d)		0	10	60	300	0	10	60	300
Cecum	Diffuse hyperplasia, mucosal epithelium	0/12	/	0/1	11/12**	0/1	/	1/1	4/4
	Single cell necrosis, absorptive epithelium	0/12	/	0/1	5/12*	0/1	/	0/1	1/4
Liver	Extramedullary haematopoiesis	2/12	2/12	3/12	2/12	6/12	6/12	7/12	5/12
	Centrilobular hypertrophy, hepatocytes	0/12	0/12	0/12	5/12*	0/12	0/12	0/12	3/12

* : $p < 0.05$; ** : $p < 0.01$

For offspring :

- *mean number of live pups (litter size) :* lower total mean number of offspring at birth, mean number of live offspring at birth and mean number of live offspring on lactation day 4 were noted at 300 mg/kg bw/d.

Table 6 : mean nb of offspring

Dose level (mg/kg bw/d)	0	10	60	300
Mean nb offspring at birth	14.3	12.5	13.5	9.1
Mean nb of live offspring at birth	14.2	12.5	13.4	9.1
Mean nb of live offspring at D 4	14.1	12.4	13.3	9.1

- *body weight data (in g) :* no significant change

Table 7 : pups body weight data (in g)

Dose level (mg/kg bw/d)		0	10	60	300
Males	PND 0	7.4	7.5	7.3	7.8
	PND 4	12.0	12.4	12.1	14.1
Females	PND 0	6.9	7.0	6.9	7.3
	PND 4	11.7	11.7	11.5	13.3

- *viability index (pups surviving 4 days/total births) :* no significant difference in viability index of PND 4

Table 8 : viability index

Dose level (mg/kg bw/d)	0	10	60	300
Viability index at D 0 (%)	99.35	100.00	99.48	100.00
Viability index at D 4 (%)	99.30	95.45	99.48	100.00

- *external, soft tissue and skeletal malformations and other relevant alterations :* no abnormalities were observed in dead offspring on LD 0 to 4 and live offspring on LD 4.
- *anogenital distance :* no effects

Table 9 : anogenital distance in mm (D 4 after birth)

Dose level (mg/kg bw/d)	0	10	60	300
Males	5.03	4.97	4.71	5.19
Females	2.42	2.26	2.27	2.44

- *necropsy :* no abnormalities were observed in either group

3.10.1.2 Extended-one generation reproductive toxicity study (Anonymous 13, 2019)

Study reference:

Anonymous 13, 2019

Detailed study summary and results:

Test type

OECD TG 443

GLP

Test substance

- BPS
- *Degree of purity :* see confidential annex

Test animals

- *Species/strain/sex :* rat / SD / both sexes
- *No. of animals per sex per dose :*
    - F0 generation parental animals : 24/sex/dose
    - F1 rearing animals, cohort 1A (reproductive PND 90) : 20/sex/dose (1 male and 1 female pup/litter)
    - F1 rearing animals, cohort 1B (F1 generation parental animals) : 24/sex/dose (1 male and 1 female pup/litter)
    - F1 rearing animals, cohort 2A (neurotoxicity PND 75-90) : 10/sex/dose (1 male or 1 female pup/litter)
    - F1 rearing animals, cohort 2B (neurotoxicity PND 22) : 10/sex/dose (1 male or 1 female pup/litter)
    - F1 rearing animals, cohort 3 (immunotoxicity) : 10/sex/dose (1 male or 1 female pup/litter)
    - Number of samples for thyroid hormones (PND 4) : 10/sex/dose
    - Number of samples for thyroid hormones and pathology (PND 22) : 10/sex/dose
- *Age and weight at the study initiation :* 5 weeks (for females) and 6 weeks old (for males)

Administration/exposure

- *route of administration :* gavage
- *duration and frequency of test/exposure period :* Daily, minimum 10 weeks after the beginning of exposure, males and females from the same dose group were mated. Shortly before weaning of the

F1 pups, the F0 males were sacrificed whereas, the F0 females were sacrificed after weaning of the F1 pups.

Before weaning of the F1 pups on PND 21, 74 animals/sex/group were randomly selected and, after weaning, placed into cohorts.

- Cohort 1A were sacrificed approximately at 13 weeks old.
- Cohort 1B were selected to produce F2 pups : minimum 10 weeks after assignment of the F1 parental animals, the males and females were mated. As for the F0 generation, F1 males were sacrificed shortly before weaning and F1 females shortly after the weaning.
- Cohort 2A were selected to examine neurotoxicity parameters and were sacrificed approximately at 11 weeks old.
- Cohort 2B were selected to examine neurotoxicity parameters and were sacrificed approximately at 3 weeks old.
- Cohort 3 were selected to examine immunotoxicity parameters and were sacrificed approximately at 8-9 weeks old.

Pups, which were not chosen for the cohorts or for blood sampling on PND 4 and 22, were sacrificed after standardization or weaning.

All pups were macroscopically examined and only animals with notable findings or abnormalities were further evaluated.

- *doses/concentration levels :* 0, 20, 60 and 180 mg/kg bw/d
- *vehicle:* 0.5% CMC

Results and discussion

For P adults :

- *number of animals at the start of the test :* 24/sex/dose
- *time of death during the study and whether animals survived to termination :* 1 female of the low dose group was sacrificed moribund on D 63, due to clinical signs (piloerection, encrusted nose, unsteady gait, hypothermia, poor general condition, labored respiration, pale skin). The necropsy of this animal revealed findings consistent with a gavage error.
- *clinical observations:* transient salivation were observed immediately after dosing in 13 males and 6 females of the highest dose during the first weeks of exposure. However, the maternal care was not affected during gestation and lactation periods.
- *water consumption :* significantly higher at the highest dose in both sexes
- *food consumption :* significantly increased in females exposed to 180 mg/kg bw/d during premating period and during GD 14-20 (up to 36 % and 8 %, respectively).

Table 10 : mean food consumption per animal and per day (in g)

	Males				Females			
Dose level (in mg/kg bw/d)	0	20	60	180	0	20	60	180
In-life period D 0-69	27.7	28.3	29.2	29.5	16.9	17.4	18.5	19.8**
GD 0-20	-	-	-	-	23.4	24.2	24.3	24.2
LD 1-21	-	-	-	-	64.5	63.9	66.9	65.1

** : p<0.01

- *body weight data :*

Table 11 : body weight data in males (in g)

Dose level (in mg/kg bw/d)		0	20	60	180
In-life period	D 0	188.4	187.9	188.6	190.0
	D 21	350.9	347.2	357.1	358.8
	D 42	433.4	426.7	435.5	434.4
	D 63	490.9	482.5	487.1	479.1
Parental period	W 0	492.5	487.2	488.4	478.7
	W 2	523.0	513.9	520.1	506.9
	W 5	544.1	535.9	563.7	551.7

Table 12 : body weight data in females (in g)

Dose level (in mg/kg bw/d)		0	20	60	180
In-life period	D 0	115.3	115.9	116.5	115.3
	D 7	141.3	144.8	148.3*	145.2
	D 14	162.8	169.9	172.4*	169.6
	D 21	184.5	192.6	193.3	190.7
	D 42	225.5	234.0	235.2	233.2
	D 63	249.1	259.0	258.1	256.4
Gestation period	GD 0	256.2	262.9	261.9	257.5
	GD 14	323.6	329.9	329.5	323.4
	GD 20	402.4	403.6	405.6	398.0
Lactation period	LD 0	300.8	310.9	310.2	304.7
	LD 10	336.2	337.4	344.2	340.9
	LD 21	316.6	324.8	327.8	322.5

* : p<0.05

- *haematological and clinical biochemistry findings :* significant change was only noted for MCH in males (1.07, 1.06, 1.09 and 1.11* fmol respectively at 0, 20, 60 and 180 mg/kg bw/d). Enzymes were not affected

Table 13 : enzymes data

	Males				Females			
Dose level (in mg/kg bw/d)	0	20	60	180	0	20	60	180
ALT (µkat/l)	0.72	0.73	0.74	2.60[A]	0.77	0.70	0.72	0.81
AST (µkat/l)	1.99	2.12	1.97	12.29[B]	1.78	1.70	1.91	1.93
ALP (µkat/l)	1.32	1.36	1.24	1.45	1.21	1.21	1.10	1.48
GGT_C (nkat/l)	25	25	25	25	25	25	25	25

[A] : S.d for ALT : 0.13, 0.12, 0.13 and 5.68 in males, respectively at 0, 20, 60 and 180 mg/kg bw/d
[B] : S.d for AST : 0.45, 0.50, 0.63 and 32.80 in males, respectively at 0, 20, 60 and 180 mg/kg bw/d

- *thyroid hormones :* no significant changes were observed
  - *T4 :* 56.15, 51.97, 54.31 and 53.04 nmol/l in males and 35.24, 37.40, 36.21 and 33.43 nmol/L in females, respectively at 0, 20, 60 and 180 mg/kg bw/d.
  - *TSH :* 8.47, 9.40, 9.05 and 8.65 µg/l in males and 5.50, 5.21, 5.54 and 4.52 µg/l in females, respectively at 0, 20, 60 and 180 mg/kg bw/d.
- *effects on sperm :*
  - *% of motile sperm :* 88, 84*, 85* and 86* % respectively at 0, 20, 60 and 180 mg/kg bw/d.
  - *Tot. spermatids/gram testis :* 100 in control vs 104 Mio/g at the highest dose
  - *Tot. sperms/gram cauda epididymis :* 732 in control vs 728 Mio/g at the highest dose
  - *% of abnormal sperms :* 5.6 in control vs 5.5 % at the highest dose
- *fertility data for males :*
  - *male mating index :* 100 % for all tested and control groups
  - *male fertility index (number of males with females pregnant/number of males placed with females) :* 96 (23/24), 91 (21/23), 100 (24/24) and 96 % (23/24) respectively at 0, 20, 60 and 180 mg/kg bw/d.
- *female reproduction data :*

Table 14 : female reproduction and delivery data

Dose level (in mg/kg bw/d)	0	20	60	180
Females mated	24	23	24	24
Female mating index (in %)	100	100	100	100
Mean mating day until DPC 0	2.0	2.3	2.2	2.3
Female fertility index (in %)	96	91	100	96
Nb. of females with liveborn pups	23	21	24	23
Nb. of females with stillborn pups	2	4	2	4
Nb. of females with all stillborn	0	0	0	0

- *number of P females cycling normally and cycle length :* mean duration of oestrus cycle : 3.9, 3.9, 3.9 and 4.1* d respectively at 0, 20, 60 and 180 mg/kg bw/d

  Mean number of days in stage : prooestrus : 2.21 d at 180 mg/kg bw/d vs 4.67 d in control

Mean number of days in stage : oestrus : 5.17 d at 180 mg/kg bw/d vs 5.12 d in control

Mean number of days in stage : metoestrus : 5.87 d at 180 mg/kg bw/d vs 5.83 d in control

Mean number of days in stage : dioestrus : 9.04 d at 180 mg/kg bw/d vs 6.33 d in control

At 20 mg/kg bw/d, 1 female exhibited a mean of cycle length of 5.3 days and one other female had a mean cycle length of 4.0 days however this female showed 1 oestrus cycle with a dioestrus period of 9 days.

At 180 mg/kg bw/d, 2 females exhibited a mean cycle length of 4.7 and 5.0 days. This last one had one cycle with a dioestrus period of 5 days.

- *duration of gestation (calculated from day 0 of pregnancy) :* 22.0 d in all tested and control groups.
- *number of implantations, corpora lutea, litter size*
    - *Total number of implantation sites :* 353, 310, 357 and 328 respectively at 0, 20, 60 and 180 mg/kg bw/d
    - *Mean number of implantation sites :* 15.3, 14.8, 14.9 and 14.3 respectively at 0, 20, 60 and 180 mg/kg bw/d
- *number of pre- and post-implantation loss*
    - *Total number of post implantation loss :* 11, 16, 32 and 35 respectively at 0, 20, 60 and 180 mg/kg bw/d
    - *Mean number of post implantation loss :* 0.5, 0.8, 1.3* and 1.5** respectively at 0, 20, 60 and 180 mg/kg bw/d
    - *Mean % of post implantation loss :* 3.1, 5.9, 9.4* and 10.5** % respectively at 0, 20, 60 and 180 mg/kg bw/d
- *necropsy findings :* Enlarged cecum was observed in 3 males of the highest dose and enlarged kidneys was noted in 6 males of the highest dose. Other findings were observed individually or equally distributed.
- *body weight at sacrifice and absolute and relative organ weight data for the parental animals:*

Table 15 : organ weight data

		Males				Females			
Dose level (in mg/kg bw/d)		0	20	60	180	0	20	60	180
FBW (in g)		521.575	514.408	521.35	507.229	272.125	278.826	275.429	273.408
Adrenal glands	Abs (mg)	54.0	55.958	58.75*	60.625*	80.208	70.391	77.208	71.625
	Rel	0.01	0.011	0.011*	0.012**	0.029	0.025	0.028	0.026
Brain	Abs (g)	2.293	2.27	2.238	2.256	2.018	2.03	2.036	2.043
	Rel	0.443	0.448	0.431	0.449	0.745	0.732	0.741	0.751
Heart	Abs (g)	1.667	1.708	1.698	1.718	1.145	1.178	1.198	1.22
	Rel	0.32	0.334	0.327	0.338	0.422	0.424	0.435	0.448
Kidneys	Abs (g)	3.543	3.391	3.673	4.124**	2.083	2.135	2.137	2.148
	Rel	0.68	0.663	0.705	0.817**	0.767	0.768	0.776	0.787
Liver	Abs (g)	12.572	13.298	13.003	12.46	8.08	8.259	8.348	8.695
	Rel	2.413	2.575	2.491	2.455	2.968	2.964	3.029	3.181**
Pituitary gland	Abs (mg)	13.542	13.583	13.875	14.417	14.375	15.13	14.833	14.625
	Rel	0.003	0.003	0.003	0.003	0.005	0.005	0.005	0.005
Spleen	Abs (g)	0.776	0.814	0.828	0.766	0.536	0.564	0.583	0.531
	Rel	0.15	0.159	0.159	0.152	0.197	0.204	0.213	0.195
Thymus	Abs (mg)	250.167	283.375	283.292*	233.708	239.167	224.391	233.625	218.875
	Rel	0.048	0.056	0.054*	0.046	0.088	0.081	0.085	0.08
Thyroid glands	Abs (mg)	24.833	25.625	24.875	25.625	15.625	18.13	17.125	16.542
	Rel	0.005	0.005	0.005	0.005	0.006	0.007	0.006	0.006
Cauda epididymis	Abs (g)	0.548	0.559	0.552	0.537	-	-	-	-
	Rel	0.106	0.111	0.106	0.107	-	-	-	-
Epididymis	Abs (g)	1.304	1.328	1.3	1.3	-	-	-	-
	Rel	0.252	0.263	0.25	0.258	-	-	-	-
Prostate	Abs (g)	1.478	1.423	1.454	1.335	-	-	-	-
	Rel	0.286	0.281	0.281	0.266	-	-	-	-
Sem. ves.	Abs (g)	1.924	1.788	1.847	1.834	-	-	-	-
	Rel	0.37	0.352	0.355	0.365	-	-	-	-
Testes	Abs (g)	3.642	3.739	3.53	3.659	-	-	-	-
	Rel	0.703	0.739	0.679	0.726	-	-	-	-
Ovaries	Abs (mg)	-	-	-	-	102.667	111.13	106.0	104.042
	Rel	-	-	-	-	0.038	0.04	0.039	0.038
Uterus	Abs (g)	-	-	-	-	0.728	0.709	0.75	0.737
	Rel	-	-	-	-	0.268	0.255	0.274	0.273

* : $p<0.05$; ** : $p<0.01$

- *histopathological findings: nature and severity :*

Table 16 : incidence of microscopic findings

		Males				Females			
Dose level (in mg/kg bw/d)		0	20	60	180	0	20	60	180
Kidneys									
Nb of animals examined		24	24	24	24	20	4	3	21
Mineralization, medulla	Inc.	0	0	1	21	14	2	1	15
	Grade 1			1	11				
	Grade 2				7				
	Grade 3				1				
	Grade 4				2				
Nuclear crowding	Inc.	0	0	0	22	0	0	0	0
	Grade 1				11				
	Grade 2				8				
	Grade 3				3				
Dilatation, tubular	Inc.	0	0	0	13	0	0	0	0
	Grade 1				7				
	Grade 2				6				

For F1 pups/litters :

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

Table 17 : litter data

Dose level (in mg/kg bw/d)	0	20	60	180
Tot. nb of pups delivered	342	294	325	293
Mean nb of pups delivered	14.9	14.0	13.5	12.7
Nb of litters	23	21	24	23
Nb of liveborn	340	289	322	285*
Nb of stillborn	2	5	3	8*

* : $p<0.05$

At 20 mg/kg bw/d, 3 females had a lower number of live pups (1 with 9 live pups (0 dead pups), 1 with 3 live pups (0 dead pups) and 1 with 5 live pups (1 dead pups)).

At 60 mg/kg bw/d, 3 females had a lower number of live pups (2 with 9 live pups (0 dead pups) and 1 with 5 live pups (1 dead pups).

At 180 mg/kg bw/d, 3 females had a lower number of live pups (2 with 9 live pups and 1 with 3 live pups).

Table 18 : mean number of live pups/litter

Dose level (in mg/kg bw/d)	0	20	60	180
D1	14.7	13.5	13.4	12.4
D4 (pre-culling)	14.6	13.3	13.3	12.3
D4 (post-culling)	10.0	9.4	9.7	9.6
D21	10.0	9.4	9.7	9.6

- *sex ratio :* 53.8/46.2, 51.6/48.4, 46.9/53.1 and 47.7/52.3 % of live males/live females at day 0, respectively at 0, 20, 60 and 180 mg/kg bw/d

  50.2/49.8, 50.3/49.7, 47.4/52.6 and 49.1/50.9 % of live males/live females at day 21, respectively at 0, 20, 60 and 180 mg/kg bw/d
- *clinical observations :* no test related effects were observed
- *viability index :*
  - *viability index (pups surviving days 0 to 4 (pre-culling)) :* 99 (336), 97 (280), 99 (319) and 99 % (283) respectively at 0, 20, 60 and 180 mg/kg bw/d
  - *lactation index (pups surviving days 4 (post-culling) to 21) :* 100 (229), 100 (197), 100 (232), 100 % (220) respectively at 0, 20, 60 and 180 mg/kg bw/d
- *mean litter or pup weight by sex and with sexes combined :*

Table 19 : pup body weight data (in g)

Dose level (in mg/kg bw/d)		0	20	60	180
D 1	Males	7.1	7.4	7.7*	7.7[A]
	Females	6.7	7.0	7.2*	7.3*
	M + F	6.9	7.2	7.5*	7.5*
D 4 (post-culling)	Males	10.5	10.9	11.5*	11.4*
	Females	9.9	10.3	10.9*	10.9*
	M + F	10.2	10.6	11.2*	11.2*
D 21	Males	54.0	56.8	57.4*	55.7
	Females	52.0	54.3	54.8*	53.7
	M + F	53.0	55.5	56.0*	54.7

* : $p<0.05$
[A] : S.d : 0.52, 0.76, 0.74 and 0.76

- *thyroid hormones :*

Table 20 : thyroid hormones data

	Males				Females			
Dose level (in mg/kg bw/d)	0	20	60	180	0	20	60	180
PND 4								
T4 (nmol/l)	27.47	23.48	25.49	25.64	24.54	28.17	24.80	24.85
TSH (µg/l)	3.87	3.67	3.79	3.98	4.15	3.54**	3.85	3.95*
PND 22								
T4 (nmol/l)	51.13	54.45	55.55	57.49	56.09	55.98	49.75	51.07
TSH (µg/l)	4.35	4.56	5.38	4.17	4.35	4.48	4.39	4.59

* : $p<0.05$; ** : $p<0.01$

- *necropsy observations :*
  - *number of pups evaluated :* 152, 122, 154 and 125 respectively at 0, 20, 60 and 180 mg/kg bw/d

- *total pup incidence :* 2 (2 with empty stomach), 2 (1 with empty stomach and 1 with post mortem autolysis), 2 (1 with haemorrhagic testis and 1 with eye(s) discoloured) and 1 (post-mortem autolysis) respectively at 0, 20, 60 and 180 mg/kg bw/d

- *anogenital distance :*

Table 21 : mean anogenital distance on D 1 (in mm)

Dose level (in mg/kg bw/d)	0	20	60	180
Male	3.59	3.67	3.61	3.63
Female	1.72	1.78	1.78	1.79

- *sexual maturation :*

Table 22 : vaginal opening : number of pups reaching criteria/number of tested (cumulated value)

Dose level (in mg/kg bw/d)	0	20	60	180
D 28	0/64	0/64	0/64	4/64
D 35	59/64	57/64	60/63	59/63
D 40	64/64	64/64	63/63	63/63
Mean days to reach criterion	32.3	32.2*	32.3	31.8
BW at day reaching criterion (in g)	105.8	112.6*	113.4*	109.9

* : $p<0.05$

Table 23 : preputial separation : number of pups reaching criteria/number of tested (cumulated value)

Dose level (in mg/kg bw/d)	0	20	60	180
D 38	0/64	1/64	2/64	0/64
D 45	54/64	54/64	55/64	50/64
D 55	64/64	64/64	64/64	64/64
Mean days to reach criterion	43.1	43.0	42.5	43.3
BW at day reaching criterion (in g)	221.1	222.8	223.3	222.5

- *presence of areolas/nipples :*
  - % of pups reaching criteria on PND 13 : 66, 72, 68 and 64 % respectively at 0, 20, 60 and 180 mg/kg bw/d
  - % of pups reaching criteria on PND 20 : 0 % at all tested and control groups. No nipples/areolae were detected in any male pups.

For cohort 1A :

- *number of animals at the start of the test :* 20/sex/dose
- *time of death during the study and whether animals survived to termination :* 1 female of the highest dose was found dead on study day 0. Necropsy revealed a slight fibrinous inflammation in the lung, focal hyperplasia in the mammary gland and an atrophic uterus.

- *clinical observations :* transient salivation was observed immediately after dosing at the highest dose in both sexes (12 males out of 20 and 14 females out of 20)
- *water consumption :* significantly higher in females at the highest dose level
- *food consumption :* significantly higher in females exposed to 180 mg/kg bw/d (up to 21% compared to control).

Table 24 : mean food consumption (in g)

	Males				Females			
Dose level (in mg/kg bw/d)	0	20	60	180	0	20	60	180
Mean D 0-56	26.2	26.0	26.9	26.4	17.2	17.6	18.3	19.7*

* : p<0.05

- *body weight data :*

Table 25 : body weight data (in g)

	Males				Females			
Dose level (in mg/kg bw/d)	0	20	60	180	0	20	60	180
D 0	86.8	86.8	85.5	85.9	77.5	78.4	79.9	78.2
D 14	208.0	203.0	204.9	203.7	149.0	153.4	159.6*	159.6*
D 21	266.4	262.7	263.9	254.0	173.9	176.1	184.2	183.2
D 28	326.7	322.0	323.5	315.5	193.5	196.0	207.3*	207.1*
D 42	408.4	404.1	408.4	394.1	226.9	228.4	237.6	241.0
D 63	488.3	490.6	472.9	459.2	264.1	256.3	265.1	277.0

* : p <0.05

- *haematological and clinical biochemistry findings if available :* Males exposed to the highest dose exhibited significant haematological changes such as higher HGB (8.7, 8.6, 8.7 and 9.0* mmol/L respectively at 0, 20, 60 and 180 mg/kg bw/d) and higher HQT (34.2, 34.3, 34.0 and 37.4* sec respectively at 0, 20, 60 and 180 mg/kg bw/d).

  Females exposed to the highest dose showed significant changes such as higher tot. prot (65.99, 65.02, 68.41 and 70.15* g/L respectively at 0, 20, 60 and 180 mg/kg bw/d), higher albumin (40.40, 40.23, 40.99 and 42.83* g/l respectively at 0, 20, 60 and 180 mg/kg bw/d).
- *thyroid hormones :*

Table 26 : thyroid hormones

	Males				Females			
Dose level (in mg/kg bw/d)	0	20	60	180	0	20	60	180
T4 (nmol/l)	72.40	64.16	63.47	60.64	38.39	37.84	38.58	39.88
TSH (µg/l)	9.61	7.08	8.61	6.48	3.23	3.64	3.49	3.93

- *Lymphocyte subpopulations in spleen at PND 90 :* No changes in the lymphocyte subpopulation cell counts in the spleen were observed (B-lymphocytes, T-lymphocytes, CD4-T-lymphocytes, CD8-T-lymphocytes and NK were examined)

- *effects on sperm*
    - *% of motile sperm :* 84, 83, 84 and 83 % respectively at 0, 20, 60 and 180 mg/kg bw/d
    - *Tot. spermatids/gram testis :* 106 in control vs 107 Mio/g at the highest dose
    - *Tot. sperms/gram cauda epididymis :* 794 in control vs 846 Mio/g at the highest dose
    - *% of abnormal sperms :* 5.2 in control vs 5.6 % at the highest dose
- *number of F1 females cycling normally and cycle length :* mean oestrus cycle duration was of 4.1 d in all tested and control groups.
- *necropsy findings :* all findings occurred either individually or were biological equally distributed.
- *body weight at sacrifice and absolute and relative organ weight data for the parental animals:*

Table 27 : organ weight data

		Males				Females			
Dose level (in mg/kg bw/d)		0	20	60	180	0	20	60	180
FBW (g)		455.095	449.15	452.61	433.11	242.17	240.59	248.375	251.237
Adrenal glands	Abs (mg)	65.0	63.2	63.6	70.5	69.05	69.15	71.5	76.737
	Rel	0.014	0.014	0.014	0.016**	0.029	0.029	0.029	0.031
Axillary lymph nodes	Abs (mg)	130.4	118.3	107.7	105.8	68.4	70.5	71.8	73.6
	Rel	0.028	0.026	0.024	0.025	0.028	0.03	0.029	0.029
Brain	Abs (g)	2.219	2.175	2.199	2.196	2.041	2.013	2.029	2.012
	Rel	0.491	0.49	0.486	0.51	0.851	0.841	0.821	0.803
Heart	Abs (g)	1.586	1.535	1.515	1.489	0.975	0.924	0.946	0.99
	Rel	0.349	0.343	0.335	0.344	0.403	0.385	0.382	0.394
Kidneys	Abs (g)	3.224	3.137	3.335	3.599**	1.797	1.791	1.86	1.91
	Rel	0.712	0.701	0.737	0.832**	0.745	0.745	0.747	0.759
Liver	Abs (g)	13.032	13.349	12.923	11.265**	6.828	6.725	6.906	7.238
	Rel	2.863	2.973	2.858	2.601**	2.814	2.794	2.78	2.88
Mesenteric lymph nodes	Abs (g)	298.4	318.7	291.6	322.9	236.5	221.1	257.4	244.9
	Rel	0.065	0.07	0.066	0.075	0.098	0.096	0.105	0.098
Pituitary gland	Abs (mg)	13.0	13.05	13.05	13.3	13.55	13.75	14.25	14.947
	Rel	0.003	0.003	0.003	0.003	0.006	0.006	0.006	0.006
Spleen	Abs (g)	0.876	0.817	0.801*	0.726**	0.524	0.494	0.529	0.502
	Rel	0.194	0.182	0.177*	0.168**	0.216	0.206	0.213	0.2
Thymus	Abs (mg)	435.7	418.45	435.35	350.85*	354.05	356.75	381.8	355.158
	Rel	0.095	0.094	0.096	0.08	0.146	0.148	0.154	0.142
Thyroid glands	Abs (mg)	24.5	26.15	23.75	23.45	16.7	17.35	15.8	16.526
	Rel	0.005	0.006	0.005	0.005	0.007	0.007	0.006	0.007
Cauda epididymis	Abs (g)	0.493	0.49	0.472	0.482	-	-	-	-
	Rel	0.109	0.11	0.104	0.111	-	-	-	-
Epididymis	Abs (g)	1.167	1.159	1.14	1.151	-	-	-	-
	Rel	0.258	0.26	0.252	0.266	-	-	-	-
Prostate	Abs (g)	1.163	1.118	1.053*	1.046**	-	-	-	-
	Rel	0.257	0.252	0.233	0.242	-	-	-	-

Sem. ves.	Abs (g)	1.353	1.254	1.285	1.258	-	-	-	-
	Rel	0.3	0.282	0.284	0.291	-	-	-	-
Testes	Abs (g)	3.655	3.56	3.69	3.63	-	-	-	-
	Rel	0.807	0.801	0.818	0.842	-	-	-	-
Ovaries	Abs (mg)	-	-	-	-	82.2	82.9	88.2	86.222
	Rel	-	-	-	-	0.034	0.034	0.036	0.034
Uterus	Abs (g)	-	-	-	-	0.707	0.709	0.716	0.823
	Rel	-	-	-	-	0.294	0.299	0.288	0.328

* : p<0.05 ; ** : p<0.01

- *histopathological findings: nature and severity :*

Table 28 : incidence of microscopic findings

		Males				Females			
Dose level (in mg/kg bw/d)		0	20	60	180	0	20	60	180
Kidneys									
Nb. of animals examined		20	20	20	20	20	1	0	20
Mineralization, medulla	Inc.	0	0	1	7	17	0	/	13
	Grade 1			1	2				
	Grade 2				2				
	Grade 3				3				
Nuclear crowding	Inc.	1	1	/	6	0	0	/	0
	Grade 1	1	1		5				
	Grade 2				1				
Dilatation, tubular	Inc.	0	0	2	7	0	0	/	0
	Grade 1			2	4				
	Grade 2				3				
Mammary gland									
Nb. of examined		20	18	20	20	20	/	/	20
Atrophy	Inc.	1	0	2	7	0	/	/	0

- *Differential ovarian follicle count :*
    - *Number of primordial follicles :* mean value of 398.60 at 180 mg/kg bw/d vs 335.10 in control group (absolute values : 7972 at 180 mg/kg bw/d vs 6702 in control group)
    - *Number of growing follicles :* mean value of 11.95 at 180 mg/kg bw/d vs 11 in control group (absolute value : 239 at 180 mg/kg bw/d vs 220 in control group)

For cohort 1B :

- *number of animals at the start of the test and mating :* 24/sex/dose
- *time of death during the study and whether animals survived to termination :* 1 female of the mid dose group was found dead on premating D3, histopathological examination of this animal was not performed.

- *clinical observations :* excessive salivation was observed immediately after exposure at the highest dose group (11 males and 9 females during the in-life period and 10 females during gestation period).
- *water consumption :* significantly higher in females of the highest dose
- *food consumption :* significantly higher in females exposed to 180 mg/kg bw/d during D 0-70.

Table 29 : mean food consumption (in g)

	Males				Females			
Dose level (in mg/kg bw/d)	0	20	60	180	0	20	60	80
D 0-70	26.9	26.6	27.4	27.1	17.7	17.7	19.1	19.9*
GD 0-20	-	-	-	-	25.7	24.9	25.6	26.1
LD 1-21	-	-	-	-	71.6	70.8	72.3	67.1

* : p<0.05

- *body weight data :*

Table 30 : male body weight data (in g)

Dose level (in mg/kg bw/d)		0	20	60	180
In-life period	D 0	79.8	80.1	82.3	78.9
	D 14	190.0	179.2	177.6*	173.7**
	D 21	253.9	250.3	260.4	248.4
	D 49	422.2	416.4	437.7	405.5
	D 70	489.2	481.8	502.7	466.8
Parental period	W 0	503.0	498.2	517.7	479.7
	W 5	564.3	559.2	579.7	541.6

* : p<0.05 ; ** : p<0.01

Table 31 : female body weight data (in g)

Dose level (in mg/kg bw/d)		0	20	60	180
In-life period	D 0	73.4	71.5	75.4	73.6
	D 21	170.9	170.7	185.8**	184.7**
	D 49	237.6	233.0	252.7*	258.4**
	D 70	265.6	260.9	280.9	284.4*
Gestation period	GD 0	276.8	270.5	292.2	291.4
	GD 14	345.9	335.1	356.3	355.7
	GD 20	426.0	412.3	436.5	415.7
Lactation period	LD 0	330.6	323.8	343.8	341.3
	LD 10	359.3	350.6	371.4	367.0
	LD 21	342.3	332.9	356.6	353.0

* : p<0.05 ; ** : p<0.01

- *male fertility data :*

Table 32 : male fertility data

Dose level (in mg/kg bw/d)	0	20	60	180
Number of males placed with females	24	24	23	24
Mating index (in %)	100	100	100	100
Number of males with pregnant females	24	24	22	23
Fertility index (in %)	100	100	96	96

- *female fertility data :*

Table 33 : female reproduction and delivery data

Dose level (in mg/kg bw/d)	0	20	60	180
Females mated	24	24	23	24
Female mating index (in %)	100	100	100	100
Mean mating day until DPC 0	3.0	2.4	2.5	3.0
Female fertility index (in %)	100	100	96	96
Number of females with liveborn pups	24	24	21	21
Number of females with stillborn pups	6	2	2	6
Number of females with all stillborn	0	0	0	0

- *number of P and F1 females cycling normally and cycle length :* mean duration of oestrus cycle : 3.9, 4.0, 4.0 and 4.5 d respectively at 0, 20, 60 and 180 mg/kg bw/d (S.d : 0.29, 0.16, 0.13 and 1.51, respectively at 0, 20, 60 and 180 mg/kg bw/d)

  Mean number of days in stage : prooestrus : 4.71, 2.83, 2.22 and 1.25 d, respectively at 0, 20, 60 and 180 mg/kg bw/d

  Mean number of days in stage : oestrus : 5.42, 5.21, 5.35 and 4.625 d, respectively at 0, 20, 60 and 180 mg/kg bw/d

  Mean number of days in stage : metoestrus : 6.0, 6.0, 6.3 and 5.875 d, respectively at 0, 20, 60 and 180 mg/kg bw/d

  Mean number of days in stage : dioestrus : 6.83, 8.375, 9.17 and 11.21 d, respectively at 0, 20, 60 and 180 mg/kg bw/d
- *duration of gestation (calculated from day 0 of pregnancy) :* 22.0, 21.9, 22.0 and 22.0 d respectively at 0, 20, 60 and 180 mg/kg bw/d
- *number of implantations, corpora lutea, litter size*
  - *Total number of implantation sites* : 364, 350, 338 and 316 respectively at 0, 20, 60 and 180 mg/kg bw/d
  - *Mean number of implantation sites :* 15.2, 14.6, 15.4 and 13.7 respectively at 0, 20, 60 and 180 mg/kg bw/d
- *number of pre- and post-implantation loss*
  - *Total number of post implantation loss :* 22, 18, 25 and 76 respectively at 0, 20, 60 and 180 mg/kg bw/d

- *Mean number of post implantation loss :* 0.9, 0.8, 1.1 and 3.3** respectively at 0, 20, 60 and 180 mg/kg bw/d
- *Mean % of post implantation loss :* 6.4, 5.3, 11.1 and 24.6** % respectively at 0, 20, 60 and 180 mg/kg bw/d

- *necropsy findings :* in males, enlarged kidneys were observed in 1 males of the mid dose and in 10 males of the highest dose.
- *body weight at sacrifice and absolute and relative organ weight data for the parental animals*

Table 34 : organ weight data

		Males				Females			
Dose level (in mg/kg bw/d)		0	20	60	180	0	20	60	180
FBW (g)		536.054	530.863	548.279	510.363	291.842	284.588	304.817*	308.2
Adrenal glands	Abs (mg)	59.792	62.625	67.708**	64.708	76.708	72.292	77.435	80.083
	Rel	0.011	0.012	0.012*	0.013**	0.026	0.026	0.025	0.026
Kidneys	Abs (g)	3.375	3.43	3.807**	4.252**	2.158	2.115	2.212	2.31*
	Rel	0.632	0.649	0.696**	0.832**	0.741	0.746	0.726	0.752
Liver	Abs (g)	14.813	15.395	14.677	13.272*	9.455	9.326	9.5	9.716
	Rel	2.758	2.902	2.669	2.6*	3.237	3.28	3.119	3.175
Pituitary gland	Abs (mg)	12.917	13.042	12.958	13.167	15.542	15.25	15.714	15.542
	Rel	0.002	0.002	0.002	0.003	0.005	0.005	0.005	0.005
Cauda epididymis	Abs (g)	0.542	0.544	0.535	0.525	-	-	-	-
	Rel	0.102	0.103	0.098	0.104	-	-	-	-
Epididymis	Abs (g)	1.324	1.347	1.319	1.308	-	-	-	-
	Rel	0.248	0.255	0.242	0.258	-	-	-	-
Prostate	Abs (g)	1.557	1.489	1.47	1.398	-	-	-	-
	Rel	0.293	0.283	0.269	0.274	-	-	-	-
Sem. ves.	Abs (g)	1.808	1.725	1.813	1.74	-	-	-	-
	Rel	0.34	0.327	0.332	0.342	-	-	-	-
Testes	Abs (g)	3.853	3.954	3.874	3.857	-	-	-	-
	Rel	0.723	0.75	0.712	0.764	-	-	-	-
Ovaries	Abs (mg)	-	-	-	-	109.542	109.5	113.217	106.833
	Rel	-	-	-	-	0.038	0.039	0.037	0.035
Uterus	Abs (g)	-	-	-	-	0.747	0.669	1.666	0.778
	Rel	-	-	-	-	0.255	0.235	0.538	0.255

* : $p<0.05$; ** : $p<0.01$

- *histopathological findings: nature and severity :* An atrophy of the mammary gland was noted in 1 male of each group (control and tested groups).

For F2 pups/litters of the cohorts 1B:

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

Table 35 : litter data

Dose level (in mg/kg bw/d)	0	20	60	180
Tot. nb of pups delivered	342	332	313	240
Mean nb of pups delivered	14.3	13.8	14.9	11.4**
Nb of litters	24	24	21	21
Nb of liveborn pups	336	330	311	234
Nb of stillborn pups	6	2	2	6

** : p<0.01

Table 36 : mean number of live pups/litter

Dose level (in mg/kg bw/d)	0	20	60	180
D 1	13.8	13.8	14.6	11.0
D 4 (preculling)	13.7	13.7	14.5	11.0
D 4 (postculling)	9.8	9.8	10.0	8.7
D 21	9.8	9.8	10.0	8.6

- *sex ratio (at day 0) :* 52.7/47.3, 52.1/47.9, 47.3/52.7 and 48.7/51.3 % of live males/live females respectively at 0, 20, 60 and 180 mg/kg bw/d
- *viability index (pups surviving 4 days/total births) :*
  - *viability index (pups surviving days 0 to 4 (pre-culling)) :* 98 (329), 100 (329), 98 (304) and 99 % (232) respectively at 0, 20, 60 and 180 mg/kg bw/d
  - *lactation index (pups surviving days 4 (post-culling) to 21) :* 100 (236), 100 (235), 100 (209) and 99 % (181) respectively at 0, 20, 60 and 180 mg/kg bw/d
- *mean litter or pup weight by sex and with sexes combined :*

Table 37 : pup body weight data (in g)

Dose level (in mg/kg bw/d)		0	20	60	180
D 1	Males	7.5	7.5	7.4	8.0
	Females	7.2	7.0	7.0	7.7*
	M + F	7.4	7.2	7.2	7.9
D 4 (post-culling)	Males	1.3	11.0	11.0	12.3
	Females	10.9	10.5	10.5	11.8
	M + F	11.1	10.7	10.8	12.1
D 21	Males	59.1	58.9	58.6	61.1
	Females	56.9	56.2	56.5	58.3
	M + F	58.1	57.5	57.5	60.0

* : p<0.05

- *necropsy observation :*
  - *number of pups evaluated :* 336, 330, 309 and 239 pups respectively at 0, 20, 60 and 180 mg/kg bw/d
  - *pup incidence* : 9 (5 with dilated renal pelvis, 3 with post mortem autolysis, 1 with small testis), 3 (2 with dilated renal pelvis, 1 with post mortem autolysis), 4 (2 with dilated renal

pelvis, 1 with post mortem autolysis, 1 with empty stomach) and 3 (2 with dilated renal pelvis, 1 with empty stomach) affected pups respectively at 0, 20, 60 and 180 mg/kg bw/d

- *mean organ weight (males + females) :*
  - *Brain :* 1.502, 1.496, 1.488 and 1.514 g respectively at 0, 20, 60 and 180 mg/kg bw/d
  - *Thymus :* 0.246, 0.229, 0.219 and 0.228 g respectively at 0, 20, 60 and 180 mg/kg bw/d
  - *Spleen :* 0.201, 0.223, 0.196 and 0.222 g respectively at 0, 20, 60 and 180 mg/kg bw/d
- *anogenital distance :*

Table 38 : mean anogenital distance on D 1 (in mm)

Dose level (in mg/kg bw/d)	0	20	60	180
Male	3.44	3.49	3.42	3.56
Female	1.67	1.67	1.65	1.71

- *presence of areolas/nipples :*
  - % of pups reaching criteria on PND 13 : 79, 76, 77 and 66 % respectively at 0, 20, 60 and 180 mg/kg bw/d
  - % of pups reaching criteria on PND 21 : 0.0 % at all tested and control groups

For cohort 2A :

- *number of animals at the start of the test :* 10/sex/dose
- *time of death during the study and whether animals survived to termination :* no mortality observed during the study period.
- *clinical observations:* excessive salivation was observed immediately after exposure in 1 female and in 3 males exposed to 180 mg/kg bw/d
- *body weight data :*

Table 39 : body weight data

	Males				Females			
Dose level (in mg/kg bw/d)	0	20	60	180	0	20	60	180
D 0	102.5	101.9	104.2	101.0	89.0	87.3	93.4	95.3
D 21	288.0	281.6	297.4	294.1	187.3	185.3	193.6	199.1
D 42	402.5	399.6	413.3	408.2	235.8	235.2	237.8	253.0

- *startle response examination at PND 24 :*
  - *Mean max. ampl.(block 1-5) :* 265.9, 188.4*, 229.8 and 272.1 in males and 218.0, 214.2, 221.6 and 225.4 in females, respectively at 0, 20, 60 and 180 mg/kg bw/d
  - *Mean latency (block 1-5) :* 19.4, 20.3, 19.6 and 19.6 msec in males and 20.7, 19.8, 21.1 and 19.2 msec in females, respectively at 0, 20, 60 and 180 mg/kg bw/d
- *FOB examination at D 75 :*

- Home cage observations : animals did not exhibit tremors, convulsions, abnormal movements. 1 females of the control group, 2 males and 3 females of the mid dose and 2 males of high dose were sitting or laying and not walking during the observation.
- Open field observations : animals did not exhibit resistance against handling, salivation, nasal discharge, lacrimation, abnormal eyes/pupil size, abnormal posture, abnormal respiration, tremors, convulsions, abnormal movements/stereotypy. 1 males of the control group and 1 males of the highest dose were not walking during the observation.
- Sensorimotor tests/reflexes : animals did show reactions during the examination the approach and touch responses. Moreover, no abnormal reactions were detected during the examination of audition, pinna reflex, coordination of movements, behaviour during handling and pain perception.

Table 40 :

	Males				Females			
Dose level (in mg/kg bw/d)	0	20	60	180	0	20	60	180
Rearing (N)	8	8	6	6	12	13	12	13
GS F (Newton)	9.7	10.2	10.5	10.3	7.8	8.0	7.4	8.6
GS H (Newton)	5.7	5.4	6.1	6.3	4.4	4.3	4.6	4.7
FST (cm)	12.6	11.6	12.8	12.0	10.1	11.4	10.4	11.1

- *Motor activity at D 75 :* Sum of the interr. 1-12 was of 2811.8, 2951.3, 2495.9 and 2487.7 in males and of 3731.3, 3685.1, 3389.9 and 3227.5 in females, respectively at 0, 20, 60 and 180 mg/kg bw/d
- *Rearing at D 75 :* Sum of the interr. 1-12 was of 528.4, 573.6, 477.3 and 482.2 and of 609.5, 584.6, 535.3 and 461.2 in females, respectively at 0, 20, 60 and 180 mg/kg bw/d
- *Morris water maze :* no difference observed in the distance to and the time spent in the target quadrant between control and treated groups.

Table 41 : morris water maze data : learning on PND 60

	Males				Females			
Dose level (in mg/kg bw/d)	0	20	60	180	0	20	60	180
Mean cumul. Distance (in cm)								
D 1	109939.4	120616.2	113809.1	119463.9	93981.0	140207.3	123301.7	154551.5
D 2	44195.3	36789.1	44854.6	46090.5	48406.2	43069.4	36504.2	41593.1
D 3	26804.5	23618.1	16086.4	24773.5	36996.6	55256.4	35006.3	34114.6
D 4	23282.4	30615.9	30908.4	41351.6	47550.5	32484.5	26717.0	31356.4
Median latency time (in ms)								
D 1	41232.0	37162.8	36791.3	45872.0	33985.3	42142.3	39123.8	69668.3
D 2	11431.0	11992.3	10572.0	12863.8	19182.0	17311.3	15481.8	15442.8
D 3	12551.3	10222.3	7784.3	8281.0	10582.8	11709.8	11652.0	13753.3
D 4	9971.5	9332.0	8992.3	8651.3	16452.5	8160.8	10001.5	14222.0

Table 42 : morris water maze data : relearning on PND 67

	Males				Females			
Dose level (in mg/kg bw/d)	0	20	60	180	0	20	60	180
Mean cumul. Distance (in cm)								
D 6	39305.2	67564.2	33109.5	42331.4	41815.2	41719.3	43567.1	33506.2
D 7	25605.5	26582.4	35749.7	31374.5	24911.5	20785.0	26228.4	29318.7
D 8	18368.6	22044.8	23446.0	19910.2	33169.2	28938.8	21488.0	32905.8
D 9	17520.7	24455.7	16109.0	25269.0	26111.0	23675.0	17311.8	28368.1
Median latency time (in ms)								
D 6	13411.3	14649.0	10961.8	12582.8	11321.8	10982.5	14851.8	12472.5
D 7	8241.8	9132.8	12343.0	8802.0	11372.8	8384.0	9132.8	9992.8
D 8	7662.0	6284.3	6271.5	8811.5	12952.0	12582.8	10461.8	11802.5
D 9	6172.3	10982.5	7150.8	5191.0	11011.3	7872.5	6854.3	10361.3

- *necropsy findings :* no treatment related effects were noted
- *body weight at sacrifice and absolute and relative organ weight data for the parental animals :*

Table 43 : brain weight data

		Males				Females			
Dose level (in mg/kg bw/d)		0	20	60	180	0	20	60	180
FBW (in g)		394.72	394.66	408.31	402.59	236.19	227.32	233.66	248.19
Brain	Abs (g)	2.262	2.166	2.223	2.242	2.047	2.02	2.033	2.077
	Rel	0.579	0.55	0.546	0.557	0.871	0.897	0.872	0.842

- *Length and width of brain :*
    - *Length :* 2.20, 2.17, 2.21 and 2.22 cm in males and 2.12, 2.12, 2.13 and 2.13 cm in females, respectively at 0, 20, 60 and 180 mg/kg bw/d
    - *Width :* 1.62, 1.61, 1.63 and 1.60 cm in males and 1.58, 1.58, 1.57 and 1.59 cm in females, respectively at 0, 20, 60 and 180 mg/kg bw/d
- *histopathological findings: nature and severity :* no treatment related effects were observed

For cohort 2B :

- *necropsy findings :* no abnormalities observed
- *body weight at sacrifice and absolute and relative organ weight data for the parental animals :*

Table 44 : brain weight data

		Males				Females			
Dose level (in mg/kg bw/d)		0	20	60	180	0	20	60	180
FBW (in g)		59.88	57.64	60.29	60.71	56.1	57.39	58.25	59.61
Brain	Abs (g)	1.828	1.783	1.855	1.819	1.757	1.74	1.751	1.801
	Rel	3.063	3.109	3.087	3.004	3.146	3.041	3.016	3.023

- *Length and width of brain :*
  - *Length :* 1.95, 1.91, 1.94 and 1.95 cm in males and 1.91, 1.91, 1.92 and 1.92 cm in females respectively at 0, 20, 60 and 180 mg/kg bw/d
  - *Width :* 1.53, 1.53, 1.53 and 1.55 cm in males and 1.51, 1.52, 1.52 and 1.51 cm in females, respectively at 0, 20, 60 and 180 mg/kg bw/d
- *histopathological findings: nature and severity :* no abnormalities observed

For cohort 3 :

- *number of animals at the start of the test :* 10/sex/dose
- *clinical observations:* no effects were observed
- *time of death during the study and whether animals survived to termination :* one female of the lowest dose was found dead on study day 18
- *body weight data :*

Table 45 : body weight data (in g)

	Males				Females			
Dose level (in mg/kg bw/d)	0	20	60	180	0	20	60	180
D 0	100.2	100.6	105.9	98.7	91.2	93.1	88.8	92.9
D 14	214.5	219.2	228.4	219.3	160.8	160.8	161.1	173.2[A]
D 28	328.8	339.9	344.1	344.6	203.7	204.8	202.4	217.4[B]

[A] : S.d : 15.7, 12.9, 21.5 and 14.2, respectively at 0, 20, 60 and 180 mg/kg bw/d
[B] : S.d : 23.3, 13.7, 25.1 and 15.3, respectively at 0, 20, 60 and 180 mg/kg bw/d

- *T-cell dependent antibody response (SRBC) at D 63 :*
  - *Males :* 3738, 3727, 4414 and 3599 U/ml respectively at 0, 20, 60 and 180 mg/kg bw/d (positive control : 927 U/ml)
  - *Females :* 13647, 8239, 9598 and 14555 U/ml respectively at 0, 20, 60 and 180 mg/kg bw/d (positive control : 1546 U/ml)
- *necropsy findings :* no treatment related effects were observed.
- *body weight at sacrifice and absolute and relative organ weight data for the parental animals :*

Table 46 : organ weight data

		Males				Females			
Dose level (in mg/kg bw/d)		0	20	60	180	0	20	60	180
FBW (g)		332.29	345.04	345.59	349.43	198.92	200.711	198.8	211.29
Spleen	Abs (g)	0.717	0.705	0.668	0.677	0.465	0.479	0.416	0.478
	Rel	0.217	0.205	0.193	0.193	0.233	0.239	0.211	0.227
Thymus	Abs (mg)	620.4	602.6	645.7	530.1	478.1	467.222	488.1	486.6
	Rel	0.187	0.176	0.187	0.152*	0.239	0.231	0.247	0.231

* : p<0.05

- *histopathological findings: nature and severity :* examination not performed

For pups not selected for cohorts :

- *necropsy findings :* no treatment related effects were observed.
- *body weight at sacrifice and absolute and relative organ weight data for the parental animals :*

Table 47 : organ weight data

		Males				Females			
Dose level (in mg/kg bw/d)		0	20	60	180	0	20	60	180
FBW (g)		56.91	58.94	62.79	61.83	56.35	60.05	60.32	57.09
Brain	Abs (g)	1.554	1.567	1.628**	1.596	1.543	1.564	1.512	1.522
	Rel	2.742	2.672	2.606	2.585	2.747	2.617	2.513**	2.677
Spleen	Abs (g)	0.238	0.293	0.284	0.285	0.242	0.267	0.276	0.266
	Rel	0.416	0.495**	0.453	0.462	0.429	0.447	0.457	0.465
Thymus	Abs (mg)	228.6	284.2**	267.2*	247.8	260.7	265.1	273.5	258.5
	Rel	0.402	0.483**	0.425	0.401	0.465	0.44	0.543	0.454

* : p<0.05 ; ** : p<0.01

- *histopathological findings: nature and severity :* no treatment related effects were noted.

3.10.1.3 Range finding study preceding the EOGRTS, similar to a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (Anonymous 14, 2017)

Study reference:

Anonymous 14, 2017

Detailed study summary and results:

Test type

Range finding study

Similar to OECD TG 422

GLP

Test substance

- 4,4'-sulphonyldiphenol
- *Degree of purity :* see confidential annex

Test animals

- *Species/strain/sex :* rat / SD / both sexes
- *No. of animals per sex per dose :* 10/sex/dose
- *Age and weight at the study initiation :* approx. 9 w for males and 10 w for females

Administration/exposure

- *Route of administration :* gavage
- *duration and frequency of test/exposure period :* daily
    - Males : 10 w
    - Females : from premating period until lactation period (until one day before necropsy)
- *doses/concentration levels :* 0, 30, 100 and 300 mg/kg bw/d
- *vehicle:* CMC

Results and discussion

For P:

- *time of death during the study and whether animals survived to termination :* no premature death was observed
- *clinical observations: description, severity, time of onset and duration :* increased incidence of excessive salivation was observed at the highest dose level
- *body weight data :* bw was reduced at 300 mg/kg bw/d (-7 % in males and -6 % in females compared to the control group)
- *haematological and clinical biochemistry findings if available :* no effects (no more information available)
- *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 :* Females exhibited prolonged oestrus. Pregnant females had a significantly lower average number of implantation sites. Moreover, post-implantation loss was significantly higher and 2 out of 8 pregnant females had complete intrauterine litter losses.

Table 48 : reproductive data

Dose level (in mg/kg bw/d)	0	30	100	300
Mean duration of oestrus cycle (d)	4.02	3.97	4.01	5.16**
Fertility index (%)	100	90	100	60
Mean nb of implantation sites	15.8	15.0	15.5	10.4**
Females without implantation sites	0	0	0	2
% of post-implantation loss	3.6	5.2	6.5	34.6*
Mean duration of gestation (d)	22	22.1	22	22
Tot. nb of pups delivered	152	127	145	65
Nb of stillborn	2	1	3	3
Mean nb of pups delivered	15.2	14.1	14.5	10.8**
Mean perinatal loss (%)	1.3	0.6	2	5.3

* : p<0.05 ; ** : p<0.01

- *effects on sperm :* not examined
- *necropsy findings :* Males exposed to 300 mg/kg bw/d exhibited dilatation of cecum (3 males out of 10), enlarged and discoloration of kidneys (9 males out of 10 for enlarge and 8 males out of 10 for discoloration) and enlarged liver (3 males out of 10).
- *body weight at sacrifice and absolute and relative organ weight data for the parental animals :* higher kidneys weight in males at the mid and high doses (+11.5 and 35 % respectively at 100 and 300 mg/kg bw/d) and higher liver weight in males at the highest dose (+11 %).

Table 49 : Organ weight data (FBW in g and organ weight in %)

	Males				Females			
Dose level (in mg/kg bw/d)	0	30	100	300	0	30	100	300
FBW	548.6	530.2	546.3	497.5*	304.5	301.8	292.6	286.6
Adrenals	0.014	0.014	0.014	0.015	0.027	0.029	0.03	0.03
Kidneys	0.662	0.692	0.748**	1.013**	0.722	0.731	0.762	0.752
Liver	2.375	2.378	2.519	2.668**	2.846	2.938	3.297[A]	2.927
Prostate	0.302	0.303	0.278	0.297	-	-	-	-
Sem. ves.	0.357	0.366	0.336	0.348	-	-	-	-
Testes	0.685	0.663	0.663	0.734	-	-	-	-
Ovaries	-	-	-	-	0.035	0.035	0.037	0.034
Uterus	-	-	-	-	0.197	0.224	0.224	0.307B

* p<0.05 ; ** : p<0.01

[A] : S.d : 0.154, 0.395, 0.677 and 0.189, respectively at 0, 30, 100 and 300 mg/kg bw/d

[B] : S.d : 0.026, 0.088, 0.099 and 0.152, respectively at 0, 30, 100 and 300 mg/kg bw/d

- *histopathological findings:*

Table 50 : incidence of microscopic data

		Males				Females			
Dose level (in mg/kg bw/d)		0	30	100	300	0	30	100	300
Cecum	Dilatation	0	0	0	3	0	0	0	0
	Thickening of wall	0	0	5	9	0	0	0	0
	Increased apoptosis	0	0	3	9	0	0	0	0
Kidneys	Degeneration/regeneration	0	0	6	10	0	0	0	0
	mineralization	0	0	2	2	1	0	0	4
	Tubular distension	0	0	5	10	0	0	0	0
Liver	Infiltration lymphoid	10	1	2	10	10	0	0	10
	Multifocal necrosis	1	0	1	1	0	0	0	0
Mammary gland	Diffuse atrophy	0	0	0	10	0	0	0	0

For F1 pups/litters (per dose):

- *clinical signs :* no effects were observed
- *mean number of live pups (litter size) :*

Table 51 : live pups data

Dose level (in mg/kg bw/d)	0	30	100	300
Tot. nb of pups delivered	152	127	145	65
Nb of stillborn	2	1	3	3
Mean nb of pups delivered	15.2	14.1	14.5	10.8**
Mean perinatal loss (%)	1.3	0.6	2	5.3

** : $p<0.01$

- *sex ratio :* no information available
- *viability index (pups surviving 4 days/total births) :* no mortality occurred (no more information available)
- *survival index at weaning* : no information available
- *mean litter or pup weight by sex and with sexes combined :* a significant bw increase (+6.6 %) was observed in male pups of the low dose at PND 21
- *external, soft tissue and skeletal malformations and other relevant alterations :* no effects (no more information available)

3.10.1.4 Range finding study preceding the EOGRTS, similar to a 28-day repeated dose toxicity study (Anonymous 15, 2017)

Study reference:

Anonymous 15, 2017

Detailed study summary and results:

Test type

Preliminary study

No guideline followed

No GLP

Test substance

- 4,4'-sulphonyldiphenol
- *Degree of purity :* see confidential annex

Test animals

- *Species/strain/sex :* rat / SD / both sexes
- *No. of animals per sex per dose :* 5/sex/dose
- *Age and weight at the study initiation :* approx. 63 D for males and 62 D for females

Administration/exposure

- *Route of administration :* gavage
- *duration and frequency of test/exposure period :* 28 d, daily
- *doses/concentration levels :* 0, 100, 300 and 600 mg/kg bw/d
- *vehicle:* 0.5 % CMC

Results and discussion

- *clinical observations :* excessive salivation (no more information available)
- *body weight data :* sign. lower bwg value was noted in males exposed to the highest dose
- *haematological and clinical biochemistry findings if available :* no information available
- *necropsy findings :* Changes were observed in males. Enlarged kidneys were noted in 3 males exposed to 300 mg/kg bw/d and in 4 males exposed to 600 mg/kg bw/d and dilatation of cecum was observed in 2 males of the highest dose.
- *body weight at sacrifice and absolute and relative organ weight data for the parental animals :* Males exhibited a significantly decrease of FBW (-9 and -12 % respectively at 300 and 600 mg/kg bw/d, compared to control). Moreover, few relative organ weights were modified. The relative kidneys weight was higher at the mid and high doses in both sexes (+33 % and +12 % respectively in males and females, compared to the control group). The relative adrenals weight was higher in males (+18 and +39 % respectively at 300 and 600 mg/kg bw/d, compared to the control group). The relative liver weight was significantly increased in females (+9 and +12 % respectively at 300 and 600 mg/kg bw/d, compared to the control group). The relative prostate and seminal vesicles weights were also modified at the highest dose (-15 % for prostate and -16 % for seminal vesicles).
  No more information available
- *histopathological findings: nature and severity :* few changes :
  - In 2, 5 and 5 males exposed respectively to 100, 300 and 600 mg/kg bw/d, minimal to moderate tubular degeneration/regeneration in kidneys was noted. Moreover, tubular hypertrophy was observed in 5 males of the highest dose (moderate hypertrophy), in 5 males

of the mid dose (minimal hypertrophy) and in 1 male of the low dose (minimal hypertrophy).

- Minimal hypertrophy/hyperplasia in the adrenal cortex was observed in 3 males exposed to 600 mg/kg bw/d.
- Centrilobular hypertrophy of the liver was noted in 1 males of the low dose (minimal hypertrophy), in 4 males of the mid dose (slight hypertrophy) and in all animals of the high dose (moderate hypertrophy in males and slight in females).
- 5 males and 2 females of the highest dose exhibited dilatation of the cecum.
- 3 males exposed to 300 mg/kg bw/d and 4 males exposed to 600 mg/kg bw/d exhibited diffuse atrophy of the mammary gland.

3.10.1.5 28-day repeated dose toxicity study including 2-weeks of recovery period (Anonymous 16, 1999)

Study reference:

Anonymous 16, 1999

Detailed study summary and results:

Test type

Similar to OECD TG 407

GLP

Test substance

- 4,4'-sulphonyldiphenol
- *Degree of purity :* see confidential annex

Test animals

- *Species/strain/sex :* rat / SD / male + female
- *No. of animals per sex per dose :* 6/sex/group for main groups + 6/sex/group for recovery groups
- *Age and weight at the study initiation :* 6 w old; 206-224 g for males and 156-180 g for females

Administration/exposure

- *route of administration :* oral, gavage
- *duration of test/exposure period :* 28 days
- *frequency of exposure :* daily
- *doses/concentration levels :* main groups : 0, 40, 200 and 1000 mg/kg bw/d
  recovery groups : 0, 200 and 1000 mg/kg bw/d
- *post exposure observation period :* 2 weeks for the recovery groups
- *vehicle :* 0.5 % aqueous solution of methylcellulose

Results and discussion

- *mortality :* 2 males, exposed to the highest dose, died (1 of the main group (at D 13) and 1 of the recovery group (at D 21)). The necropsy of these animals revealed a dilatation of the cecum and signs of haemorrhage in the intestinal tract.
- *description of clinical signs :* an abdominal distension was observed at the highest dose in 1 female after 15 D and in 5 females after 28 D. During the recovery period, this effect disappeared.
- *body weight and body weight changes :* significant lower bw value at the highest dose were noted in males during the dosing period. After 14 D of the recovery period, this change was not significant.

Table 52 : body weight data during dosing and recovery period (in grams)

	Males				Females			
Dose level (mg/kg bw/d)	0	40	200	1000	0	40	200	1000
Exposure period								
D 1	217	214	215	215	165	165	166	168
D 14	330	324	325	281**	216	216	210	206
D 28	409	402	401	337**	258	256	244	240
BWG (1 – 28)	192	187	186	122**	93	91	78*	72**
Recovery period								
D 1	398	/	411	330**	258	/	250	242
D 10	435	/	445	384*	279	/	271	259
D 14	457	/	465	416	286	/	278	269
BWG (1 – 14)	59	/	54	86**	28	/	28	27

* : p<0.05 ; ** : p<0.01

- *food consumption :* significant decrease at 1000 mg/kg bw/d in both sexes (more marked in males)
- *haematological findings :* significant decrease of RBC, haemoglobin and haematocrit were observed in both sexes at the highest dose level. Moreover, a significant reduced prothrombin time was observed in females.

In all dose levels, a significant lower value of mean corpuscular haemoglobin concentration was observed in females.

Table 53 : haematological findings

		males				females			
Dose level (mg/kg bw/d)		0	40	200	1000	0	40	200	1000
Dosing period	RBC (10^4/mm³)	770	764	763	687*	773	766	776	705**
	Hb (g/dL)	15.9	15.9	15.8	14.3**	16.2	15.9	15.9	13.9**
	Ht (%)	47	47	46	42**	47	47	47	42**
	MCHC (%)	34.1	33.9	34.1	33.7	34.5	34.0*	33.9*	33.6*
	PT (sec)	12.9	13.4	13.6	12.9	12.0	12.2	12.0	11.4*
Recovery period	RBC (10^4/mm³)	804	/	793	735**	809	/	801	762
	Hb (g/dL)	16.0	/	15.9	15.3	16.2	/	15.8	15.2**
	Ht (%)	47	/	47	45	47	/	47	45
	MCHC (%)	33.8	/	33.9	33.8	34.1	/	33.3*	33.4
	PT (sec)	13.5	/	13.2	11.8**	11.9	/	11.6	11.7

* : p<0.05 ; ** : p<0.01

- *clinical biochemistry findings :* in males, a significant higher ALP activity and a significant lower LDH activity were noted at the highest dose level. Whereas, in females, a significant increase of total protein, albumin and calcium and a significant decrease of total cholesterol were observed.

Table 54 : blood chemical findings

		males				females			
Dose level (mg/kg bw/d)		0	40	200	1000	0	40	200	1000
Dosing period	GOT (IU/L)	44	47	55	56	64	59	57	52
	LDH (IU/L)	43	40	39	25**	27	25	27	28
	ALP (IU/L)	307	298	289	424*	205	209	197	222
	Tot. prot. (g/dL)	6.3	6.1	6.1	6.4	6.2	6.2	6.3	7.2**
	Albumin (g/dL)	3.7	3.7	3.6	3.8	3.7	3.8	3.8	4.2**
	Tot. chol. (mg/dL)	65	61	64	25**	85	64	71	42**
	Ca (mg/dL)	9.4	9.3	9.4	9.7	9.5	9.4	9.5	10.1**
Recovery period	GOT (IU/L)	43	/	43	24*	60	/	57	55
	LDH (IU/L)	53	/	40	55	23	/	26	23
	ALP (IU/L)	249	/	260	271	152	/	144	142
	Tot. prot. (g/dL)	6.4	/	6.4	6.1	6.8	/	6.5	6.7
	Albumin (g/dL)	3.7	/	3.8	3.7	4.0	/	3.9	4.0
	Tot. chol. (mg/dL)	72	/	73	69	86	/	75	100
	Ca (mg/dL)	9.1	/	9.1	9.1	9.4	/	9.2	9.3

* : $p<0.05$; ** : $p<0.01$

- *gross pathology findings :*
  - cases necropsied at the end of the dosing period : a dilatation of cecum was observed in all animals of the highest dose level (5 out of 5 males and 6 out of 6 females at 1000 mg/kg bw/d vs 0 out of 6 males and 0 out of 6 females in control group and in the low and mid dose groups).
  - cases necropsied at the end of the recovery period : dark red spots in the glandular stomach were observed in 2 females of the mid dose level and 2 females of the high dose level. No abnormalities were seen in males.
- *Organ weight :* few changes were observed (see table 55 and 56)
  - cases necropsied at the end of the dosing period :

Table 55 : absolute and relative organ weights data

		males				females			
Dose level (mg/kg bw/d)		0	40	200	1000	0	40	200	1000
Nb of animals examined		6	6	6	6	6	6	6	6
FBW (g)		389	369	364	311**	234	235	223	218
Adrenals	Abs.(mg)	70	71	66	101**	72	74	65	74
	Rel.	18	19	18	33**	31	32	29	34
Brain	Abs. (g)	2.07	2.06	2.07	1.99	1.90	1.89	1.86	1.82
	Rel.	0.53	0.56	0.57	0.64**	0.81	0.80	0.84	0.84
Heart	Abs. (g)	1.30	1.18	1.21	0.99**	0.84	0.87	0.79	0.81
	Rel.	0.34	0.32	0.33	0.32	0.36	0.37	0.36	0.37
Kidneys	Abs. (g)	2.79	2.68	3.09	2.76	1.84	1.76	1.73	1.83
	Rel.	0.72	0.73	0.85**	0.89**	0.79	0.75	0.77	0.84
Liver	Abs. (g)	11.98	11.35	11.14	10.94	7.23	6.83	6.99	8.46
	Rel.	3.07	3.07	3.06	3.54**	3.09	2.90	3.14	3.89**
Lung	Abs. (g)	1.33	1.28	1.33	1.13*	1.09	1.06	1.04	0.92**
	Rel.	0.34	0.35	0.37	0.36	0.47	0.45	0.47	0.42**
Thymus	Abs. (mg)	438	428	493	252**	475	521	441	259**
	Rel.	113	117	135	82	203	221	199	119**
Testes	Abs. (g)	3.07	2.94	3.06	2.96	-	-	-	-
	Rel.	0.79	0.81	0.84	0.96**	-	-	-	-
Ovaries	Abs. (mg)	-	-	-	-	86.1	92.0	85.1	76.5
	Rel.	-	-	-	-	36.7	38.9	38.1	34.9

* : p<0.05 ; ** : p<0.01

- cases necropsied at the end of the recovery period :

Table 56 : absolute and relative organ weight data

		Males			Females		
Dose level (mg/kg bw/d)		0	200	1000	0	200	1000
Nb of animal examined		6	6	6	6	6	6
FBW (g)		425	432	376*	265	257	246
Adrenals	Abs.(mg)	59	60	80**	71	69	75
	Rel.	14	14	21**	27	27	31
Brain	Abs. (g)	2.05	2.05	1.99	1.89	1.95	1.88
	Rel.	0.48	0.48	0.53*	0.71	0.76	0.77
Heart	Abs. (g)	1.33	1.38	1.29	0.88	0.90	0.90
	Rel.	0.31	0.32	0.34*	0.33	0.35	0.37*
Kidneys	Abs. (g)	2.76	3.21**	2.71	1.84	1.86	1.98
	Rel.	0.65	0.75**	0.72*	0.70	0.73	0.81
Liver	Abs. (g)	12.86	13.32	11.03	7.40	7.25	7.95
	Rel.	3.02	3.07	2.93	2.79	2.82	3.21*
Lung	Abs. (g)	1.30	1.37	1.24	1.05	1.06	1.00
	Rel.	0.31	0.32	0.33*	0.40	0.41	0.41
Thymus	Abs. (mg)	434	415	336	407	342	335
	Rel.	103	96	91	154	134	134

Testes	Abs. (g)	3.29	3.20	3.15	-	-	-
	Rel.	0.78	0.74	0.84	-	-	-
Ovaries	Abs. (mg)	-	-	-	77.0	75.4	70.4
	Rel.	-	-	-	29.1	29.4	28.7

* : p<0.05 ; ** : p<0.01

- *histopathology findings :* few significant changes were observed in animals at the end of dosing period (see table 57). These changes were not present at the end of recovery period (see table 58).
    - cases necropsied at the end of the dosing period :

Table 57 : histopathological findings

			Males				Females			
Dose level (mg/kg bw/d)			0	40	200	1000	0	40	200	1000
cecum	Hyperplasia mucosa	Inc.	0/6	0/6	6*/6	5*/5	0/6	0/6	5**/6	6**/6
		grade 1	/	/	2	2	/	/	4	5
		grade 2	/	/	4	3	/	/	1	1
	Single cell necrosis, mucosal epithelium	Inc.	0/6	0/6	4*/6	5*/5	0/6	0/6	4*/6	4*/6
		grade 1	/	/	3	2	/	/	4	1
		grade 2	/	/	1	3	/	/	/	2
		grade 3	/	/	/	/	/	/	/	1
liver	Hypertrophy centrilobular		0/6	0/6	0/6	3*/5 (3 slight)	0/6	0/6	0/6	3/6 (3 slight)
adrenals	Hypertrophy, zona fasciculata		0/6	0/6	0/6	4*/5 (4 slight)	0/6	0/6	0/6	0/6
thymus	atrophy		0/6	0/6	0/6	4**/5 (4 slight)	0/6	0/6	0/6	4*/6 (4 slight)
femur	Increase spongy bone		0/6	0/6	0/6	5**/5 (5 slight)	0/6	0/6	0/6	4*/6 (4 slight)

P : present ; grade 1 : slight ; grade 2 : mild ; grade 3 : moderate ; * : p<0.05 ; ** : p<0.01

- *cases necropsied at the end of the recovery period :*

Table 58 : histopathological findings

			Males			Females		
Dose level (mg/kg bw/d)			0	200	1000	0	200	1000
cecum	Hyperplasia, mucosa	Inc.	0/6	1/6	3/5	0/6	1/6	1/6
		grade 1	/	/	1	/	/	1
		grade 2	/	1	2	/	1	/
	Single cell necrosis, mucosal epithelium	Inc.	0/6	1/6	3/5	0/6	0/6	0/6
		grade 1	/	1	2	/	/	/
		grade 2	/	/	1	/	/	/
liver	microgranuloma		0/6	0/6	2/5 (2 slight)	2/6	/	2/6
femur	Increase spongy bone		0/6	0/6	1/5 (1 slight)	0/6	0/6	4*/6 (4 slight)

P : present ; grade 1 : slight ; grade 2 : mild ; * : p<0.05

3.10.1.6 90-day repeated dose toxicity study (Anonymous 17, 2014)

Study reference:

Anonymous 17, 2014

Detailed study summary and results:

Test type

According to OECD TG 408

GLP

Test substance

- 4,4'-sulphonyldiphenol
- *Degree of purity :* see confidential annex

Test animals

- *Species/strain/sex :* rat / Wistar / males + females
- *No. of animals per sex per dose :* 10/sex/dose
- *Age and weight at the study initiation :* approx. 42 d

Administration/exposure

- *route of administration :* gavage
- *duration of test/exposure period :* 90 days
- *frequency of exposure :* daily
- *doses/concentration levels :* 0, 100, 300 and 1000 mg/kg bw/d (for males, the highest dose changed to 600 mg/kg bw/d onwards 70 days)
- *vehicle:* 1 % CMC

Results and discussion

- *mortality and time to death :* no animal died
- *description, severity, time of onset and duration of clinical signs :* soft and discoloured faeces and salivation were noted in all animals of the mid and high dose.
- *body weight and body weight changes :* a lower bw was observed in male at the mid and highest dose level. This decreased was significant at the highest dose.

Table 59 : body weight and body weight gain data (in g)

	Males				Females			
Dose level (mg/kg bw/d)	0	100	300	1000/600	0	100	300	1000
D 0	158.4	157.1	158.1	158.2	126.1	127.0	126.0	126.7
D 7	203.3	199.9	198.0	189.9**	143.7	147.0	144.0	142.7
D 42	351.4	343.8	326.0	294.3**	208.4	204.7	202.8	205.2
D 91	417.1	400.7	377.3	334.7**	237.3	231.7	225.0	222.5
BWG (D 0-91)	258.7	243.6	219.2*	176.4**	111.2	104.6	99.0	95.9

* : $p < 0.05$; ** : $p < 0.01$

- *food consumption :* lower food consumption was observed in males at 1000 mg/kg bw/d (-18 % from days 7 to 63). After the reduction of the dose, the food consumption was within the usual range.
- *sensory activity, grip strength and motor activity assessments :* no test substance related effects were observed
- *ophthalmologic findings :* no effects
- *haematological findings :* RBC counts and haemoglobin values were decreased at the highest dose in both sexes. Additionally, lower haematocrit value and mean corpuscular haemoglobin concentration were observed in females at 1000 mg/kg bw/d. In males, higher mean corpuscular volume value, relative reticulocyte counts and neutrophiles and lower WBC counts were noted at the highest dose.

Table 60 : haematological findings (examined at the end of the administration period)

	Males				Females			
Dose level (in mg/kg bw/d)	0	100	300	1000/600	0	100	300	1000
RBC (tera/L)	8.71	8.83	8.46	8.08**	7.89	7.82	7.76	7.45**
Hb (mmol/L)	9.0	9.0	8.8	8.6**	8.8	8.6	8.5	8.0**
Ht (L/L)	0.427	0.426	0.420	0.412	0.408	0.406	0.402	0.380**
MCV (fL)	49.1	48.2	49.6	51.0**	51.8	52.0	51.8	51.0
MCHC (mmol/L)	21.05	21.17	20.97	20.95	21.62	21.28	21.24*	21.07**
RET (%)	1.5	1.2	1.6	1.9*	1.8	2.0	2.2	2.3
WBC (giga/L)	5.51	5.11	4.59*	4.28**	4.09	4.35	3.85	3.56

* : $p < 0.05$; ** : $p < 0.01$

- *clinical biochemistry findings:* some modification were noted (see table 61)

Table 61 : enzyme data (examined at the end of the administration period)

	Males				Females			
Dose level (in mg/kg bw/d)	0	100	300	1000/600	0	100	300	1000
ALT (µkat/l)	0.68	0.80	0.91**	0.92	0.58	0.63	0.58	0.79
AST (µkat/l)	1.63	1.42	1.77	1.81	1.38	1.54	1.36	1.19
ALP (µkat/l)	1.25	1.43	1.40	1.41	0.66	0.55	0.69	1.01*
GGT_C (nkat/l)	0	0	0	0	0	0	0	0
Chol (mmol/L)	1.85	1.65	1.23**	1.03**	1.62	1.56	1.30	1.33
Trig (mmol/L)	0.97	1.53**	1.48**	2.32**	0.72	0.81	0.79	0.99

* : $p < 0.05$; ** : $p < 0.01$

- *gross pathology findings :* Dilatation of cecum was noted in all males at the highest dose level. While the liver was enlarged bw/d in 8 females out of 10 exposed to 1000 mg/kg. An uterus dilatation was observed in 3 females at 300 mg/kg bw/d.
- *organ weight :* reproductive organs weights was significantly decreased in males at 1000 mg/kg bw/d (epididymides and testes (also at the mid dose level). Significant lower brain and thymus weights were observed in both sexes at the highest dose whereas a higher adrenal glands weight was noted.

Table 62 : organ weight (relative weight in %)

		Males				Females			
Dose level (mg/kg bw/d)		0	100	300	1000/600	0	100	300	1000
FBW (g)		394.02	376.95	356.6**	311.89**	221.72	214.72	207.95	205.6
Adrenal glands (g)	Abs	64.5	59.1	63.7	90.1**	65.6	64.5	74.6	80.4**
	Rel	0.016	0.016	0.018	0.029**	0.03	0.03	0.036*	0.039**
Brain (g)	Abs	2.212	2.098**	2.074**	2.084**	2.007	1.992	1.99	1.913*
	Rel	0.565	0.564	0.583	0.675**	0.91	0.931	0.962	0.932
Heart (g)	Abs	1.115	1.039	1.026*	0.958**	0.752	0.739	0.755	0.763
	Rel	0.284	0.277	0.288	0.309*	0.341	0.344	0.364	0.371*
Kidneys (g)	Abs	2.507	2.646	2.762	2.485	1.5	1.489	1.584	1.644*
	Rel	0.636	0.702*	0.775**	0.795**	0.679	0.695	0.765*	0.799**
Liver (g)	Abs	8.936	8.402	8.415	8.347	5.106	5.39	5.688	7.043**
	Rel	2.269	2.226	2.359	2.676**	2.297	2.502	2.75**	3.433**
Spleen (g)	Abs	0.628	0.585	0.535**	0.595	0.44	0.447	0.465	0.454
	Rel	0.16	0.156	0.15	0.19**	0.198	0.209	0.224**	0.22*
Thymus (mg)	Abs	327.5	269.4	271.3	226.1**	303.2	292.4	245.3	222.7**
	Rel	0.084	0.071	0.076	0.073	0.136	0.136	0.118	0.108*
Epididymides (g)	Abs	1.209	1.16	1.126	1.072**	-	-	-	-
	Rel	0.308	0.31	0.316	0.346**	-	-	-	-
Testes (g)	Abs	3.914	3.862	3.636*	3.592*	-	-	-	-
	Rel	0.999	1.035	1.021	1.162**	-	-	-	-
Ovaries (mg)	Abs	-	-	-	-	104.7	104.0	106.9	126.9
	Rel	-	-	-	-	0.047	0.048	0.052	0.061*
Uterus (g)	Abs	-	-	-	-	0.724	0.864	1.284	0.648
	Rel	-	-	-	-	0.332	0.41	0.615	0.315

* : $p < 0.05$; ** : $p < 0.01$

- *histopathology findings:* effects were revealed in few organs.

Table 63 : histopathological findings

		Grade	Males				Females			
Dose level (mg/kg bw/d)			0	100	300	1000/600	0	100	300	1000
Adrenal cortex	Hypertrophy/hyperplasia	Inc	0/10	0/10	0/10	8/10	0/10	0/10	0/10	0/10
Cecum	Dilatation	Inc	0/10	0/10	0/10	10/10	0/10	0/10	1/10	10/10
	Parasite(s) in lumen	Inc	0/10	0/10	0/10	1/10	0/10	0/10	0/10	0/10
	Increased apoptosis	Inc	0/10	3/10	4/10	7/10	0/10	1/10	4/10	7/10
Kidneys	Mineralization, medulla	Inc	0/10	7/10	9/10	6/10	5/10	NE	NE	3/10
		1	/	4	6	6	3			2
		2	/	3	2	/	2			1
		3	/	/	1	/	/			/
	Tubules, basophilic	Inc	8/10	8/10	9/10	8/10	2/10	NE	NE	3/10
Liver	Centrilobular hypertrophy	Inc	0/10	0/10	0/10	0/10	0/10	2/10	5/10	10/10
		1	/	/	/	/	/	1	1	/

		2	/	/	/	/	/	1	3	/
		3	/	/	/	/	/	/	1	10
	Hyperplasia, bile duct	Inc	0/10	0/10	0/10	0/10	0/10	0/10	0/10	2/10
	Cellular alteration	Inc	0/10	1/10	0/10	2/10	1/10	1/10	1/10	6/10
Mammary gland	Atrophy multifocal	Inc	0/10	0/10	7/10	10/10	0/10	NE	NE	0/10
		1	/	/	7	/	/			/
		2	/	/	/	4	/			/
		3	/	/	/	2	/			/
		4	/	/	/	3	/			/
		5	/	/	/	1	/			/
Spleen	Haematopoeisis extramedullary	Inc	0/10	0/10	0/10	8/10	2/10	1/10	4/10	10/10
		1	/	/	/	5	2	1	4	3
		2	/	/	/	3	/	/	/	7
Uterus	Squamous metaplasia	Inc	-	-	-	-	0/10	2/10	2/10	5/10
		1	-	-	-	-	/	2	2	4
		2	-	-	-	-	/	/	/	1
	Dilatation of horn(s)	Inc	-	-	-	-	0/10	0/10	3/10	0/10

P : present ; grade 1 : minimal ; grade 2 : slight ; grade 3 : moderate ; grade 4 : marked (severe) ; grade 5 : massive (extreme)

3.10.1.7 13-day repeated dose toxicity study (Anonymous 18, 1973)

Study reference:

Anonymous 18, 1973

Detailed study summary and results:

Test type

No guideline followed

No GLP

Only short abstract available

Test substance

- 4,4'-sulphonyldiphenol
- *Degree of purity :* see confidential annex

Test animals

- *Species/strain/sex :* rat / not specified / male
- *No. of animals per sex per dose :* 5 males/dose

Administration/exposure

- *route of administration :* diet
- *duration of test/exposure period :* 13 days
- *frequency of test/exposure period :* daily
- *doses/concentration levels :* 0, 0.1 and 1 % (approx. 0, 97 and 810 mg/kg bw/d)
- *vehicle:* 1 % corn oil

Results and discussion

- *mortality :* no effects

- *clinical signs :* no effects
- *body weight and body weight changes :* greatly depressed at the highest dose (no more information available)
- *haematological findings:* slight increase in RBC count, haemoglobin concentration and haematocrit were observed at the highest dose. The slight increase in haemoglobin concentration was already observed at the low dose level. (no more information available)
- *clinical biochemistry findings:* a lower aspartate aminotransferase value was noted at 1 % (no more information available)
- *gross pathology findings:* an adipose tissue atrophy was noted in 1 male exposed to 0.1 % and in all 5 males exposed to 1 %.
- *organ weight :* lower absolute liver and kidney weights were observed at the highest dose (no more information available).
- *histopathology findings:* adipose tissue atrophy and cytoplasmatic basophilia of epithelium of the renal distal convoluted tubule were noted at 1 % (no more information available).

3.10.1.8 Prenatal developmental toxicity Study (Anonymous 19, 2014)

Study reference:

Anonymous 19, 2014

Detailed study summary and results:

Test type

According to OECD TG 414

GLP

Test substance

- 4,4'-sulphonyldiphenol
- *Degree of purity :* see confidential annex

Test animals

- *Species/strain/sex :* rat / Wistar / pregnant female
- *No. of animals per sex per dose :* 25 pregnant females/dose

Administration/exposure

- *Route of administration :* gavage
- *duration of test/exposure period :* GD 6 – 19 (sacrifice of the animals at GD 20)
- *doses/concentration levels :* 0, 30, 100 and 300 mg/kg bw/d
- *vehicle:* 1 % carboxymethylcellulose

Results and discussion

For dams :

- *mortality :* no mortality observed

- *clinical observations :* at the highest dose level, 7 out of 25 females exhibited excessive salivation after exposure.
- *body weight data :* bwg calculated for the entire treatment period (GD 6 – 19) was significantly reduced at the highest dose. The corrected body weight gain (terminal body weight on GD 20 minus uterus weight minus body weight on GD 6) was reduced at the highest dose (40.9, 43.7, 40.0 and 36.9 g respectively at 0, 30, 100 and 300 mg/kg bw/d).

Table 64 : body weight and body weight gain data (in g)

Dose level (mg/kg bw/d)	0	30	100	300
GD 0	164.9	167.5	168.7	165.6
GD 6	195.9	199.1	199.2	198.3
GD 15	239.3	243.5	240.6	236.1
GD 20	295.9	302.4	297.8	291.0
GD 8 - 10	9.6	9.3	9.4	6.8*
GD 6 - 19	85.2	89.8	84.3	78.6*
GD 0 - 20	131.0	134.9	129.1	125.4
Corrected bwg	40.9	43.7	40.0	36.9

* p<0.05 ; Only pregnant dams with scheduled sacrifice (GD 20) were used for the calculation of bw.
1 female of the highest dose was excluded as this rat was not pregnant

- *food consumption :* lower food consumption observed during the entire treatment period at 300 mg/kg bw/d (-8 % compared to control group).
- *organ weight data :* no substance related effect for the mean gravid uterus weight

Table 65 : Mean gravid uterine weight and net maternal bwg (in g)

Dose level (mg/kg bw/d)	0	30	100	300
Gravid uterus (in g)	59.1	59.6	58.7	55.8
Carcass	236.8	242.8	239.1	235.2
Terminal bw minus uterine weight	236.8	242.8	239.1	235.2

- *reproduction data :*
  - number of corpora lutea : no effects
  - number of implantation sites : no effects
  - number of pre- and post-implantation loss : no effects
  - number of resorptions and viable foetuses : no effects

Table 66 : reproduction data

Dose level (mg/kg bw/d)	0	30	100	300
Nb of females mated	25	25	25	25
Conception rate (%)	100	100	100	96 (24/25)
Nb of females aborted	0	0	0	0
Nb of dams with viable foetuses	25	25	25	24
Mean nb. of corpora lutea	11.5	11.8	11.7	11.4
Mean nb. of implantation sites	11.1	11.0	11.1	10.8
Mean pre implantation loss (%)	3.6	6.1	5.4	5.3
Mean post implantation loss (%)	4.7	3.9	3.9	6.3
Mean early resorption	0.5	0.4	0.4	0.6
Mean late resorption	0.0	0.0	0.1	0.0
Mean total resorption	0.5	0.4	0.5	0.7
Nb of dead foetuses	0	0	0	0
Mean live foetuses (females/males)	10.6 (5.2/5.4)	10.6 (5.0/5.6)	10.6 (6.0/4.6)	10.1 (4.8/5.3)

- *necropsy findings :* no substance-related necropsy findings (1 female exhibited a diaphragmatic hernia (females which failed to be pregnant), another one had dilated renal pelvis and another one had hemometra)
- *placenta weight :* no effects (mean placental weight of all viable foetuses : 0.45, 0.46, 0.45 and 0.47 g respectively at 0, 30, 100 and 300 mg/kg bw/d)

For foetuses :

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

Table 67 : pups data

Dose level (mg/kg bw/d)	0	30	100	300
Nb of litter evaluated	25	25	25	24
Nb of live foetuses evaluated	264	265	265	243
Mean nb. of live foetuses	10.6	10.6	10.6	10.1
Nb of dead foetuses evaluated	0	0	0	0

- *sex ratio :* no effect (48.9/51.1, 47.2/52.8, 56.6/43.4 and 47.3/52.7 % of females/males respectively at 0, 30, 100 and 300 mg/kg bw/d)
- *mean litter or pup weight by sex and with sexes combined :* the mean foetal weight was comparable to control group

Table 68 : mean foetal weight (in g)

Dose level (mg/kg bw/d)	0	30	100	300
Foetal weight of all viable foetuses	3.6	3.6	3.4	3.4
Foetal weight of male foetuses	3.6	3.7	3.5	3.5
Foetal weight of female foetuses	3.5	3.5	3.4	3.3

- *external, soft tissue and skeletal malformations and other relevant alterations :*

- *external examination :*
  - *malformations :* 1 foetus at 100 mg/kg bw/d presented multiple external malformations (misshapen head and absent face (anophthalmia, astomia, anotia)).
  - *variations :* no external variation were found
- *soft tissue examination :*
  - *malformations :* no soft tissue malformations were recorded
  - *variations :* effects were observed such as dilated renal pelvis, dilated ureter, however these effects were also noted in control groups.

Table 69 : total soft tissue variations

Dose level (mg/kg bw/d)	0	30	100	300
Nb of litter	25	25	25	24
Nb of foetuses	127	128	125	116
Foetal incidence : nb (%)	7 (5.5)	5 (3.9)	12 (9.6)	10 (8.6)
Litter incidence : nb (%)	7 (28)	4 (16)	9 (36)	9 (38)
Mean affected foetuses/litter	6.1	4.1	9.1	8.5

- *Skeletal examination :*
  - *malformations :* effects were observed in all groups. These effects affected the skull, sternum and forelimbs.

Table 70 : total skeletal malformations

Dose level (mg/kg bw/d)	0	30	100	300
Nb of litter	25	25	25	24
Nb of foetuses	137	137	140	127
Foetal incidence : nb (%)	1 (0.7)	0.0	3 (2.1)	5 (3.9)
Litter incidence : nb (%)	1 (4.0)	0.0	3 (12)	5 (21)
Mean affected foetuses/litter	0.7	0.0	2.8	4.3*

* $p<0.05$

0 mg/kg bw/d :1 female exhibit shortened humerus

30 mg/kg bw/d : none

100 mg/kg bw/d : 1 male with multiple skeletal malformations, 1 male with shortened scapula, 1 female with shortened humerus

300 mg/kg bw/d : 2 male exhibited malpositioned and bipartite sternebra, 1 male with shortened humerus, 1 female with misshapen basisphenoid and 1 female with misshapen tuberositas deltoidea

  - *variations :* effects were recorded in all groups

Table 71 : skeletal variations data

Dose level (mg/kg bw/d)	0	30	100	300	HCD mean % (range)
Nb of litter	25	25	25	24	/
Nb of foetuses	137	137	140	127	/
Total skeletal variations					
Foetal incidence : nb (%)	136 (99)	135 (99)	139 (99)	127 (100)	/
Litter incidence : nb (%)	25 (100)	25 (100)	25 (100)	24 (100)	/
Mean affected foetuses/litter	99.2	98.3	98.7	100.0	/
Incidence of significant increased foetal skeletal variations (mean % of affected foetus/litter)					
Incomplete ossification of supraoccipital (unchanged cartilage)	34.1	35.2	37.6	45.2*	43.5 (10.3 – 64.3)
Dumbbell ossification of thoracic centrum (unchanged cartilage)	0.7	3.0	0.0	5.6**	6.9 (0.0 – 14.5)
Unossified sternebra (unchanged cartilage)	1.5	5.0	4.6	11.0**	8.2 (2.6 – 20.7)
Incomplete ossification of pubis (cartilage present)	0.0	0.8	2.0*	1.7	0.3 (0.0 – 2.4)
Incomplete ossification of ischium (cartilage present)	0.0	0.0	2.0*	1.7	0.2 (0.0 – 0.8)

* : $p<0.05$; ** : $p<0.01$

3.10.2 Human data

No information available

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

No information available

3.11 Specific target organ toxicity – single exposure

Not evaluated in this dossier

3.12 Specific target organ toxicity – repeated exposure

Not evaluated in this dossier

3.13 Aspiration hazard

Not evaluated in this dossier

4 ENVIRONMENTAL HAZARDS

Not evaluated in this dossier

5 ABBREVIATIONS

* : $p<0.05$

** : $p<0.01$

Abs. : absolute

AGD : anogenital distance

ALP : alkaline phosphatase

ALT : alanine aminotransferase

Ampl. : amplitude

Approx. : approximately

AST : aspartate aminotransferase

BW : body weight

BWG : body weight gain

Ca : calcium

Chol : cholesterol

CMC : carboxymethylcellulose

Cumul. : cumulative

DIT : developmental immunotoxicity study

DNT : developmental neurotoxicity study

DPC : day post-coitum

DS : dossier submitter

EOGRTS : extended one generation reproductive toxicity study

Epith. : epithelium

FBW : final body weight

FOB : functional observational battery

F : female

GD : gestional day

GGT_C = serum-γ-glutamyltransferase

GLP : good laboratory practice

GOT : glutamic oxaloacetic transaminase

HCD : historical control data

HGB or Hb : haemoglobin

HQT : prothrombin time (hepato Quick's test)

HT : hematocrit

Inc. : incidence

LD : lactation day

LDH : lactate dehydrogenase

M : male

Max. : maximum

MCH : mean corpuscular haemoglobin

MCHC : mean corpuscular haemoglobin concentration

Mio : million

Nb or no : number

NK : natural killer

P : parental

PND : post-natal day

PT : prothrombine time

RBC : red blood cell

Rel : relative

Ret : reticulocyte

S.d : standard deviation

SD : Sprague-Dawley

Sem. ves. : seminal vesicle

Sign : significant

SRBC = sheep red blood cell

T4 = total thyroxine

TSH = thyroid-stimulating hormone

TG : test guideline

Tot : total

Tot. chol. : total cholesterol

Tot. prot. : total protein

Trig : triglyceride

WBC : white blood cell