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:

propyl 4-hydroxybenzoate

EC Number: 202-307-7

CAS Number: 94-13-3

Index Number: 607-RST-VW-Y

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Hazard class not assessed in this CLH report

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Not evaluated in this dossier

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Hazard class not assessed in this CLH report

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Hazard class not assessed in this CLH report

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Hazard class not assessed in this CLH report

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Hazard class not assessed in this CLH report

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Hazard class not assessed in this CLH report

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Hazard class not assessed in this CLH report

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Hazard class not assessed in this CLH report

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Hazard class not assessed in this CLH report

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Study reference:

Anonymous, 2020

Detailed study summary and results:

Test type

OECD TG 443

GLP

Cohorts: 1A and 1B for reproductive and developmental toxicity testing

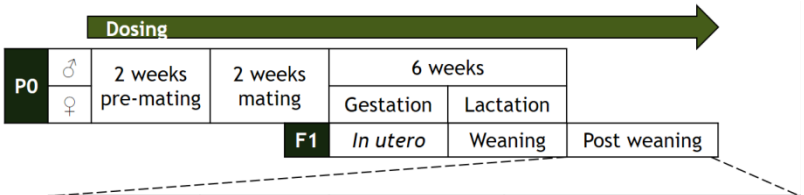
2A: neurobehavior testing and neurohistopathology assessment

2B: neurohistopathology assessment at PND 21 or 22

3: for developmental immunotoxicity testing on PND 56

4: for learning and memory testing

Figure 1: study design (Anonymous, 2020)



	Target	N Animals	Age at necropsy	Endpoint
F1A	Reproductive	20 M + 20 F	13 weeks	Organ weight
F1B	Reproductive	20 M + 20 F	14-25 weeks	Repro - Generation F2
F2A	Neurotox	10 M + 10 F	11-12 weeks	Audit. startle + motor activ.
F2B	Neurotox	10 M + 10 F	3 weeks	Neuropathology
F3	Immunotox	10 M + 10 F	8 weeks	Antibody response
F4	Neurotox	10 M + 10 F	6 weeks	Learning and Memory

Test substance

- Propylparaben
- *Degree of purity:* 99.7 %

Test animals

- *Species/strain/sex :* rats / Wistar / both sexes
- *No. of animals per sex per dose :* parental generation : 30/sex/group for control and high dose and 25/sex/dose for low and mid doses

  Cohort 1A : 20/sex/dose

  Cohort 1B : 20/sex/dose

  Cohort 2A : 10/sex/dose

  Cohort 2B : 10/sex/dose

Cohort 3 : 10/sex/dose

Cohort 4 : 10/sex/dose

- *Age and weight at the study initiation :* 13 – 14 weeks old (at study initiation), 306 – 358 g for males and 177 – 241 g for females (at allocation to the group).

Administration/exposure

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

  F0 parental : Males : min. 10 weeks (14 d of pre-mating, max 14 d of mating and until terminal sacrifice)

  Females : 14 d of pre-mating, max 14 d of mating, during gestation and until weaning (PND 21)

  F1 selected offspring : from weaning (PND 22) to terminal sacrifice of the respective cohorts :

  Cohort 1A : sacrifice at week 13 of age (approx. 10 weeks of treatment)

  Cohort 1B : exposure until weaning of F2 (sacrifice approx. to week 20 – 25 of age)

  Cohort 2A : approx. to week 12 of age (approx. 9 weeks of treatment)

  Cohort 2B : at weaning

  Cohort 3 : at 8 week of age (approx. 5 weeks of treatment)

  Cohort 4 : sacrifice at PND 35 - 42
- *doses/concentration levels, rationale for dose level selection :* 0, 100, 300 and 1000 mg/kg bw/d
- *control group and treatment :* positive control : cyclophosphamide and hemocyanin megathura crenulata
- *vehicle:* 1 % of hydroxyethyl-cellulose

Results and discussion

For P (F0) :

- *time of death during the study and whether animals survived to termination :* 3 females of low dose group were sacrificed at PMD 6, GD 21 and PND 4, and 1 female of the mid dose was euthanized at PND 18 (for animal welfare reasons).
- *clinical observations:* at the highest dose, 22 males exhibited increased salivation and all males exhibited moving bedding. No other treatment related effect were noted. In females, increased salivation and moving bedding were observed at the mid and high dose (in 4 and 24 females for salivation and in 5 and 30 females for moving bedding, respectively).
- *body weight data :*

Table 1 : body weight data (in g)

Dose level (in mg/kg bw/d)	0	100	300	1000
Males				

Nb examined		30	25	25	30
D1		370.30	376.56	370.20	371.13
D21		394.87	398.56	390.64	392.73
D49		429.70	426.68	419.00	422.87
D70		449.63	443.08	438.16	440.70
Females					
Premating period	D1	227.30 (n=30)	229.72 (n=25)	229.28 (n=25)	224.07 (n=30)
	D14	232.97 (n=30)	235.71 (n=24)	235.92 (n=25)	230.37 (n=30)
Gestation period	D0	232.5 (n=26)	236.95 (n=21)	237.35 (n=23)	230.54 (n=26)
	D20	337.54 (n=24)	349.76 (n=21)	338.43 (n=23)	341.93 (n=27)
Lactation period	D0	263.92 (n=26)	268.27 (n=22)	267.23 (n=22)	266.68 (n=28)
	D7	286.81 (n=26)	288.33 (n=21)	281.59 (n=22)	280.75 (n=28)
	D21	286.72 (n=25)	289.05 (n=21)	288.90 (n=21)	287.36 (n=28)

- *haematological findings :*

Table 2 : haematological findings (at week 11)

	Males				Females			
Dose level (in mg/kg bw/d)	0	100	300	1000	0	100	300	1000
Nb examined	10	10	10	10	10	10	9	10
WBC (10^9/l)	4.944	4.832	5.462	5.366	3.973	3.388	3.311	2.413*
RBC (10^{12}/l)	9.064	9.262	9.478	9.289	7.534	7.691	7.616	7.258
Hg (g/dl)	16.14	16.29	16.54	15.22	14.63	14.86	14.74	14.30
Ht (%)	48.05	48.24	49.48	48.87	44.79	44.59	44.10	42.46*
MCV (fl)	53.03	52.10	52.24	52.67	59.55	58.02	57.93	58.52
MCH (pg)	17.81	17.608	17.448	16.393	19.44	19.31	19.39	19.71
MCHC (g/dl)	33.572	33.778	33.412	31.097	32.64	33.31	33.47*	33.69**
Plt (10^9/l)	571.9	577.6	549.9	552.6	743.0	744.7	695.9	674.1
PT (sec)					21.98	22.41 (n=9)	23.43*	23.27
aPTT (sec)					12.07	11.93	14.34	9.96

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

- *clinical biochemistry findings :*

Table 3 : clinical chemistry findings (at week 11)

	Males	Females

Dose level (in mg/kg bw/d)	0	100	300	1000	0	100	300	1000
Nb examined	10	10	10	10	10	10	9	10
ALAT (U/l)	38.52	38.83	36.30	35.83	58.51	72.16	71.50	84.91*
ASAT (U/L)	91.99	93.89	85.54	84.16	118.85	115.80	108.26	120.45
ALP (U/l)	161.04	146.744	92.816***	96.901***	299.188	406.993	391.252	405.849
TBA (µmol/l)	16.107	7.925*	15.661	9.483* (N=9)	22.374	29.679	19.423	23.411
Urea (mmol/l)	6.359	6.768	5.874	5.065*	10.237	9.629	9.536	9.965

* : $p < 0.05$; *** : $p < 0.001$

- *hormone analysis :*

Table 4 : hormone data

	Males				Females			
Dose level (in mg/kg bw/d)	0	100	300	1000	0	100	300	1000
T4 (nmol/l)	64.73 (n=10)	69.87 (n=10)	78.67 (n=10)	68.59 (n=10)	54.96 (n=9)	56.36 (n=10)	59.12 (n=9)	53.27 (n=10)
TSH (pg/ml)	2616.33 (n=10)	2963.83 (n=8)	2447.93 (n=8)	2288.95 (n=10)	1634.46 (n=8)	2015.93 (n=7)	2037.14 (n=7)	3801.42* (n=8)

* : $p < 0.05$

- *effects on sperm*

Table 5 : sperm parameters

Dose level (in mg/kg bw/d)		0	100	300	1000
Motility	Motile count (%)	77.05 (n=30)	77.60 (n=30)	77.98 (n=25)	72.67 (n=30)
	Static count (%)	22.97 (n=30)	22.40 (n=25)	22.02 (n=25)	24.00 (n=30)
	Rapid (%)	60.85 (n=30)	57.34 (n=25)	60.68 (n=25)	55.75 (n=30)
Testicular sperm count	Million sperms/g	113.5 (n=30)	115.5 (n=25)	124.0 (n=25)	114.9 (n=30)
N examined		24	0	0	24
Sperm morphology	Amorphous head	0.0	/	/	0.0
	Head only	2.46	/	/	2.63
	Bent tail	2.17	/	/	2.38
	Broken tail	0.42	/	/	0.08
	Coiled tail	0.25	/	/	0.08

	Tail only	2.96	/	/	**8.17**
Nb of sperms evaluated		200.00	/	/	200.00
Total nb of abnormal sperms		8.25	/	/	13.33
Total nb of normal sperms		191.75	/	/	186.67
% of abnormal		4.13	/	/	6.67

- *mean cycle length :* 4.07, 4.05, 4.02 and 4.01 days, respectively at 0, 100, 300 and 1000 mg/kg bw/d (n = 30, 24, 25 and 30, respectively at 0, 100, 300 and 1000 mg/kg bw/d)
- *precoital interval (number of days until mating and number of oestrous periods until mating) :* 1.90, 2.30, 2.33 and 2.31 days, respectively at 0, 100, 300 and 1000 mg/kg bw/d (n = 26, 21, 22 and 27, respectively at 0, 100, 300 and 1000 mg/kg bw/d)
- *duration of gestation (calculated from day 0 of pregnancy) :* 22.35, 22.29, 22.18 and 22.22 days, respectively at 0, 100, 300 and 1000 mg/kg bw/d (n = 30, 23, 24 and 29, respectively at 0, 100, 300 and 1000 mg/kg bw/d)
- *mean number of corpora lutea :* 11.62, 12.59, 12.35, 12.04, respectively at 0, 100, 300 and 1000 mg/kg bw/d (n = 26, 22, 23 and 27, respectively at 0, 100, 300 and 1000 mg/kg bw/d)
- *mean number of implantations sites :* 11.12, 12.14, 11.70 and 11.67, respectively at 0, 100, 300 and 1000 mg/kg bw/d (n = 26, 22, 23 and 27, respectively at 0, 100, 300 and 1000 mg/kg bw/d)
- *number of pre- and post-implantation loss :*
  - pre : 4.88, 3.30, 5.42 and 3.20 %, respectively at 0, 100, 300 and 1000 mg/kg bw/d (n = 26, 22, 23 and 27, respectively at 0, 100, 300 and 1000 mg/kg bw/d)
  - post : 5.99, 7.79, 4.76 and 8.98 %, respectievela t 0, 100, 300 and 1000 mg/kg bw/d (n = 26, 22, 22 and 27, respectively at 0, 100, 300 and 1000 mg/kg bw/d)
- *number of dams with abortions, early deliveries, stillbirths, resorptions and/or dead foetuses :*

Table 6 : mean number of live births, still births and runts

Dose level (in mg/kg bw/d)	0	100	300	1000
Mean nb of live births	10.50	11.18	10.70	10.89
Mean nb of still births	0.04	0.14	0.00	0.11
Mean nb of runts	0.00	0.05	0.00	0.11

- *mean number of births (alive and dead) :*

Table 7 : mean number of births (alive and dead pups)

Dose level (in mg/kg bw/d)	0	100	300	1000
Mean total nb of pups	10.54	11.32	10.70	11.00
Mean nb of males	5.46	5.59	5.96	5.68

Mean nb of females	5.08	2.73	4.74	5.32

- *necropsy findings :* only spontaneous gross pathological changes observed, not treatment related.
- *body weight at sacrifice and absolute and relative organ weight data for the parental animals :*

Table 8 : organ weight (in g or %)

		Males				Females			
Dose level (in mg/kg bw/d)		0	100	300	1000	0	100	300	1000
Nb animals examined		30	25	25	30	30	22[A]	24	30
FBW		454.97	452.16	443.88	445.27	280.13	285.50	279.29	283.13
Adrenal glands	Abs	0.065	0.060	0.055	0.057	0.089	0.098	0.092	0.091
	Rela	0.014	0.013	0.013	0.013	0.032	0.034	0.033	0.032
Brain	Abs	2.17	2.18	2.19	2.19	1.932	1.909	1.925	1.908
	Rela	0.48	0.48	0.49	0.49	0.693	0.971	0.696	0.681
Heart	Abs	1.199	1.198	1.157	1.139	0.904	0.901	0.893	0.911
	Rela	0.265	0.265	0.261	0.256	0.324	0.316	0.321	0.323
Liver	Abs	12.897	12.453	12.051	11.767	12.164	12.849	12.524	13.117
	Rela	2.841	2.751	2.716	2.644**	4.311	4.493	4.470	4.616
Kidneys	Abs	2.794	2.821	2.760	2.692	1.896	1.921	1.920	1.949
	Rela	0.619	0.624	0.623	0.605	0.676	0.673	0.689	0.692
Pituitary gland	Abs	0.0096	0.0097	0.0095	0.0091	0.012	0.012	0.013	0.012
	Rela	0.002	0.002	0.002	0.002	0.004	0.004	0.005	0.004
Spleen	Abs	0.816	0.835	0.793	0.806	0.679	0.750	1.305	0.702
	Rela	0.180	0.185	0.179	0.182	0.243	0.263	0.474	0.250
Thymus	Abs	0.386	0.398	0.350	0.336	0.242	0.188	0.201	0.186*
	Rela	0.085	0.089	0.079	0.075	0.088	0.067	0.074	0.067*
Thyroid/ parathyroid	Abs	0.036	0.033	0.032	0.032	0.031	0.033	0.032	0.033
	Rela	0.008	0.007	0.007	0.007	0.011	0.012	0.012	0.012
Epididymides L.	Abs	0.818	0.786	0.799	0.787				
	Rela	0.181	0.174	0.181	0.177				
Epididymides R.	Abs	0.830	0.777	0.827	0.790				
	Rela	0.184	0.173	0.187	0.177				
Testis L.	Abs	1.917	1.909	1.954	1.938				
	Rela	0.424	0.423	0.442	0.436				
Testis R.	Abs	1.903	1.883	1.929	1.894				
	Rela	0.421	0.418	0.436	0.426				

Prostate with s and c	Abs	3.281	3.226	3.008	2.856**				
	Rela	0.727	0.716	0.678	0.643**				
Ovaries	Abs					0.108	0.096	0.101	0.096
	Rela					0.039	0.034	0.037	0.034
Implantation sites	Abs					9.633	11.636	10.917	10.867
	Rela					3.372	4.070	3.890	3.795
Uterus with cervix	Abs					0.670	0.673	0.708	0.596
	Rela					0.252	0.236	0.264	0.213
Corpora lutea	Abs					10.067	12.091	11.542	11.200
	Rela					3.524	4.228	4.112	3.915

* : $p < 0.05$; ** : $p < 0.01$; [A] : n = 21 for thymus weight

- *testis weight :*

Table 9 : Testis weight

Dose level (in mg/kg bw/d)	0	100	300	1000
Nb examined	30	25	30	30
Testis weight (g)	1.976	1.974	1.997	1.994
Tunica albuginea (g)	0.149	0.164	0.155	0.158
Parenchyma weight (g)	1.827	1.810	1.842	1.836

- *histopathological findings:* no treatment related effect observed

For F1 pups/litters (per dose):

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

Table 10 : mean number of births (alive and dead pups)

Dose level (in mg/kg bw/d)	0	100	300	1000
Nb of litter examined	26	22	23	28
Mean total nb of pups	10.54	11.32	10.70	11.00
Mean nb of males	5.46	5.59	5.96	5.68
Mean nb of females	5.08	2.73	4.74	5.32

- *mean number of alive births :* 10.50, 11.18, 10.70 and 10.89, respectively at 0, 100, 300 and 1000 mg/kg bw/d (n = 26, 22, 23 and 28, respectively at 0, 100, 300 and 1000 mg/kg bw/d)
- *live birth index :* 94.01, 92.21, 95.24 and 91.02 %, respectively at 0, 100, 300 and 1000 mg/kg bw/d (n = 26, 21, 22 and 27, respectively at 0, 100, 300 and 1000 mg/kg bw/d)

- *sex ratio m/f (alive and dead births) :* 1.36, 1.17, 1.46 and 1.25 m/f, respectively at 0, 100, 300 and 1000 mg/kg bw/d
- *viability index (pups surviving 4 days/total births) and survival index at weaning :*
    - PND 0 – 4 : 98.34, 98.92, 99.59 and 99.01 %, respectively at 0, 100, 300 and 1000 mg/kg bw/d (n = 26, 21, 22 and 27, respectively at 0, 100, 300 and 1000 mg/kg bw/d)
    - PND 4 – 13 (after interim sacrifice) : 100.00, 100.00, 100.00 and 99.63 %, respectively at 0, 100, 300 and 1000 mg/kg bw/d (n = 26, 21, 22 and 27, respectively at 0, 100, 300 and 1000 mg/kg bw/d)
    - PND 13 (after interim sacrifice) – 21 : 99.62, 100.00, 98.50 and 99.69 %, respectively at 0, 100, 300 and 1000 mg/kg bw/d (n = 26, 21, 21 and 27, respectively at 0, 100, 300 and 1000 mg/kg bw/d)
- *Litter data :*

Table 11 : litter data (PND 4 to PND 21)

Dose level (in mg/kg bw/d)	0	100	300	1000
Number of litter examined	26	22	23	28
PND 4 (before interim sacrifice)				
Mean nb of live pups	10.31	11.29	10.65	10.79
Mean nb of males	5.31	5.62	5.96	5.54
Mean nb of females	5.00	5.67	4.70	5.25
Sex ratio (m/f)	1.36	1.19	1.47	1.23
PND 4 (after interim sacrifice)				
Mean nb of live pups	8.77	9.38	8.91	9.36
PND 7				
Mean nb of live pups	8.77	9.38	8.91	9.36
Mean nb of males	4.50	4.67	5.09	4.82
Mean nb of females	4.27	4.71	3.83	4.54
Sex ratio (m/f)	1.45	1.26	1.83	1.33
PND 13 (before interim sacrifice)				
Mean nb of live pups	8.77	9.38	8.91	9.32
Mean nb of males	4.50	4.67	5.09	4.79
Mean nb of females	4.27	4.71	3.83	4.54
Sex ratio (m/f)	1.45	1.26	1.70	1.32
PND 13 (after interim sacrifice)				
Mean nb of live pups	8.38	9.38	8.91	8.96
PND 21				

Mean nb of live pups	8.35	9.38	8.95	8.93
Mean nb of males	4.31	4.67	5.05	4.57
Mean nb of females	4.04	4.71	3.91	4.36
Sex ratio (m/f)	1.45	1.26	1.58	1.34

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

Table 12 : Mean pup bw and litter weight (in g)

	Mean pup bw				Mean litter weight			
Dose level (in mg/kg bw/d)	0	100	300	1000	0	100	300	1000
PND 0	6.54 (n=26)	6.49 (n=22)	6.46 (n=22)	6.31 (n=27)	67.54 (n=26)	72.11 (n=22)	71.78 (n=22)	71.01 (n=27)
PND 4	11.60 (n=26)	11.29 (n=21)	11.27 (n=22)	11.37 (n=27)	116.95 (n=26)	125.35 (n=22)	123.73 (n=22)	126.37 (n=27)
PND 7	17.61 (n=26)	16.94 (n=21)	16.94 (n=22)	16.62 (n=27)	150.32 (n=26)	156.04 (n=21)	155.22 (n=22)	159.47 (n=27)
PND 14	32.81 (n=26)	31.21 (n=21)	31.07 (n=22)	29.68** (n=27)	268.02 (n=0)	286.36 (n=21)	280.82 (n=22)	271.98 (n=27)
PND 21	52.27 (n=26)	49.87 (n=21)	49.88 (n=21)	49.12 (n=27)	427.05 (n=26)	459.07 (n=21)	461.31 (n=21)	446.27 (n=27)

- *AGD :*

Table 13 : AGD and nipple retention

Dose level (in mg/kg bw/d)	0	100	300	1000
Males				
Nb examined pups	142	123	137	159
AGD (in mm)	2.84	2.78	2.73	2.71*
Relative AGD	1.51	1.48	1.46	1.46
Nb of pup nipple retention on PND 12	0.23	0.35	0.21	0.04*
Females				
Nb examined pups	132	126	109	149
AGD (in mm)	1.26	1.15***	1.13***	1.12***
Relative AGD	0.68	0.62***	0.61***	0.61***

* : $p < 0.05$; *** : $p < 0.001$

- *Hormone analysis at PND 4 :*
    - T4 : 35.64, 32.35, 37.36 and 32.75 nmol/l, respectively at 0, 100, 300 and 1000 mg/kg bw/d (n = 10, 10, 9 and 10, respectively at 0, 100, 300 and 1000 mg/kg bw/d)
    - TSH : 485.96, 645.29, 472.17 and 545.72 pg/ml, respectively at 0, 100, 300 and 1000 mg/kg bw/d (n = 8, 9, 7 and 8, respectively at 0, 100, 300 and 1000 mg/kg bw/d)
- *Hormone analysis at PND 21 :*
    - Males :
        - T4 : 82.70, 79.01, 74.55 and 74.03 nmol/l, respectively at 0, 100, 300 and 1000 mg/kg bw/d (n = 8, 8, 6 and 8, respectively at 0, 100, 300 and 1000 mg/kg bw/d)
        - TSH : 971.70, 687.24, 751.43 and 711.05 pg/ml, respectively at 0, 100, 300 and 1000 mg/kg bw/d (n = 8, 7, 6 and 9, respectively at 0, 100, 300 and 1000 mg/kg bw/d)
    - Females :
        - T4 : 65.20, 79.44, 75.69 and 75.63 nmol/l, respectively at 0, 100, 300 and 1000 mg/kg bw/d (n = 6, 10, 8 and 7, respectively at 0, 100, 300 and 1000 mg/kg bw/d)
        - TSH : 1152.33, 1537.38, 968.41 and 672.30 pg/ml, respectively at 0, 100, 300 and 1000 mg/kg bw/d (n = 6, 7, 8 and 5, respectively at 0, 100, 300 and 1000 mg/kg bw/d)
- *Macroscopic findings (examination PND 21) :*
    - Males : enlarged spleen : 2/10, 3/10, 5/10 and 0/10, respectively at 0, 100, 300 and 1000 mg/kg bw/d
    - Females : enlarged spleen : 2/6, 3/10, 0/8 and 4/10, respectively at 0, 100, 300 and 1000 mg/kg bw/d ; short tail in 1 females of the highest dose
- *Organ weight (PND 21) :*

Table 14 : pups organ weight (in g or %)

		Males				Females			
Dose level (in mg/kg bw/d)		0	100	300	1000	0	100	300	1000
Nb examined		10	10	10	10	6	10	8	10
FBW		50.77	48.24	48.98	49.62	47.57	47.49	41.80	49.13
Brain	Abs	1.510	1.479	1.465	1.499	1.454	1.482	1.437	1.451
	Rela	3.047	3.110	3.003	3.044	3.084	3.154	3.454	2.980
Spleen	Abs	0.238	0.229	0.362	0.246	0.199	0.236	0.194	0.251
	Rela	0.464	0.476	0.726	0.491	0.419	0.494	0.466	0.508
Thymus	Abs	0.242	0.218	0.200	0.203	0.246	0.231	0.230	0.218
	Rela	0.474	0.453	0.407	0.410	0.517	0.489	0.548	0.446

For Cohort 1A (F1) :

- *number of animals :* 20 per dose
- *time of death during the study and whether animals survived to termination :* 1 male of the mid dose and 2 males and 2 females of the highest dose were found dead.
- *clinical observations: description, severity, time of onset and duration :* clinical signs such as moving the bedding was observed in 17 males and 7 females at the highest dose
- *body weight data :*

Table 15 : body weight data (in g)

	Males				Females			
Dose level (in mg/kg b/d)	0	100	300	1000	0	100	300	1000
D1	55.4	52.9	52.8	49.8**	54.6	51.4	50.7	49.2**
D29	220.7	224.7	218.0	212.2	156.4	163.2	158.6	160.8
D64	339.4	342.8	331.8	312.3**	210.6	218.8	213.7	214.4

** : $p < 0.01$

- *food consumption :* no significant difference
- *haematological findings :*

Table 16 : haematological data (at week 11)

	Males				Females			
Dose level (in mg/kg bw/d)	0	100	300	1000	0	100	300	1000
Nb examined	10	10	10	10	10	9	10	10
Ht (%)	47.63	48.16	49.28	48.97	43.89	44.51	46.84**	45.92*
Hg (g/dL)	16.02	16.33	16.45	16.76**	14.71	15.16	15.87***	15.55*
RBC (1^{12}/L)	8.845	9.036	9.017	9.285	7.960	8.038	8.515*	8.425
MCV (fL)	53.92	53.29	54.68	52.79	55.20	55.42	55.07	54.58
MCH (pg)	18.14	18.06	18.26	18.07	18.49	18.88	18.66	18.48
Plt (1^9/L)	701.4	681.3	659.9	613.9**	669.2	794.2	678.6	679.5
WBC (1^9/L)	5.376	5.580	6.660*	6.998**	2.907	4.734**	5.544***	4.479*
PT (sec)	21.49	21.58	21.94	21.74	22.33 (n=9)	21.84 (n=8)	22.95	24.19**
aPTT (sec)	9.88	9.44	9.49	9.14	9.94 (n=9)	10.34 (n=9)	10.11	9.51

* : $p < 0.05$; ** : $p < 0.01$; *** : $p < 0.001$

- *clinical biochemistry findings :*

Table 17 : clinical biochemistry findings (at week 11)

	Males				Females			
Dose level (in mg/kg bw/d)	0	100	300	1000	0	100	300	1000
Nb examined	10	10	10	10	10	9	10	10
ALAT (U/L)	38.34	41.10	38.99	38.12	33.31	34.14	31.79	28.55
ASAT (U/L)	88.56	90.26	86.05	75.63	94.94	77.14	82.10	74.06
ALP (U/L)	199.282	186.161	174.775	154.887	138.394	113.083	78.795**	80.986**

** : $p < 0.01$

- *Hormones :*

Table 18 : thyroid hormone data

	Males				Females			
Dose level (in mg/kg bw/d)	0	100	300	1000	0	100	300	1000
Nb examined	10	10	10	10	10	10	10	10
T4 (nmol/L)	82.15	85.10	81.21 (n=9)	79.32	53.20	58.60	67.08*	68.85**
TSH (pg/ml)	1912.58	2387.28	2307.35	4001.28	1730.85	3304.06	1352.69 (n=9)	1369.46 (n=9)

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

- *mean balano-preputial separation :* 32.32, 31.75, 31.75 and 31.45 PND, respectively at 0, 100, 300 and 1000 mg/kg bw/d (bw on the day of balano preputial separation : 117.60, 112.00, 108.0* and 105.10** g, respectively at 0, 100, 300 and 1000 mg/kg bw/d) (n = 20 for all groups)
- *mean vaginal opening :* 30.20, 30.55, 30.75 and 30.50 days, respectively at 0, 100, 300 and 1000 mg/kg bw/ (bw on the day of vaginal opening 96.30, 95.70, 94.30, 91.80 g, respectively at 0, 100, 300 and 1000 mg/kg bw/d)
- *number of days from VO to first E+ smear :* 3.90, 2.45, 2.25 and 2.95 days, respectively at 0, 100, 300 and 1000 mg/kg bw/d (n = 20 for control, low and mid dose groups and 19 animals for highest dose)
- *effects on male reproductive parameters :*

Table 19 : male reproductive parameters

Dose level (in mg/kg bw/d)	0	100	300	1000

Weight	Nb examined	20	20	19	18
	Testes weight (g)	1.817	1.782	1.839	1.677
	Tunica albuginea weight (g)	0.139	0.119	0.139	0.126
	Calculated parenchyma weight (g)	1.678	1.663	1.700	1.552
Sperm motility	Nb examined	20	20	19	18
	Motile count (%)	79.10	78.33	78.87	72.42
	Static count (%)	20.90	21.68	21.13	27.58
	Rapid (%)	64.83	62.88	62.13	58.11
Sperm count	Nb examined	18	19	18	16
	Mean testicular sperm count	127.6	126.8	131.5	137.2
Sperm morphology	Nb examined	20	0	0	18
	Total nb of abnormal sperms	10.35	/	/	19.06
	Total nb of normal sperms	189.65	/	/	180.94
	% normal	94.83	/	/	90.47

- *number of females cycling normally and cycle length :* (n = 20, 20, 20 and 18, respectively at 0, 100, 300 and 1000 mg/kg bw/d)
    - mean cycle length : 3.97, 4.00, 3.98 and 4.09 days, respectively 0, 100, 300 and 1000 mg/kg bw/d
    - mean number of normal cycles : 2.45, 2.50, 2.35 and 2.17, respectively at 0, 100, 300 and 1000 mg/kg bw/d
- *mean lymphocyte count in spleen :*
    - male : 331, 363, 360 and 415 lymphocytes x10^6/organ (g), respectively at 0, 100, 300 and 1000 mg/kg bw/d (St. De. : 172, 114, 61 and 129)
    - female : 333, 422, 359 and 406 lymphocytes x10^6/organ (g), respectively at 0, 100, 300 and 1000 mg/kg bw/d (St. De. : 125, 154, 103 and 148)
- *T cell count in spleen :*
    - Male : 121, 138, 143 and 175 T cell x10^6/organ (g), respectively at 0, 100, 300 and 1000 mg/kg bw/d (St. De. : 50, 49, 33 and 72)
    - Female : 127, 166, 149 and 169 T cell x10^6/organ (g), respectively at 0, 100, 300 and 1000 mg/kg bw/d (St. De. : 48, 65, 40 and 45)
- *CD4 T cell count in spleen :*
    - Male : 83, 94, 93 and 121 CD4 T cells x10^6/organ (g), respectively at 0, 100, 300 and 1000 mg/kg bw/d (St. De. : 40, 31, 17 and 44)
    - Female : 85, 113, 96 and 114 CD4 T cells x10^6/organ (g), respectively at 0, 100, 300 and 1000 mg/kg bw/d (St. De. : 34, 50, 30 and 33)

- CD8 T cell count in spleen :
    - Male : 35, 41, 47 and 51 CD8 T cells x10^6/organ (g), respectively at 0, 100, 300 and 1000 mg/kg bw/d (St. De. : 12, 21, 18 and 28)
    - Female : 38, 49, 49 and 52 CD8 T cells x10^6/organ (g), respectively at 0, 100, 300 and 1000 mg/kg bw/d (St. De. : 18, 18, 15 and 13)
- *NK cell count in spleen :*
    - Male : 12, 13, 14 and 16 NK cells x10^6/organ (g), respectively at 0, 100, 300 and 1000 mg/kg bw/d (St. De. : 8, 4, 3 and 5)
    - Female : 12, 15, 14 and 16 NK cells x10^6/organ (g), respectively at 0, 100, 300 and 1000 mg/kg bw/d (St. De. : 6, 5, 3 and 6)
- *BC cell count in spleen :*
    - Male : 133, 145, 130 and 140 B cells x10^6/organ (g), respectively at 0, 100, 300 and 1000 mg/kg bw/d (St. D. : 88, 51, 22 and 32)
    - Female : 132, 157, 126 and 146 B cells x10^6/organ (g), respectively at 0, 100, 300 and 1000 mg/kg bw/d (St. De. : 49, 60, 47 and 61)
- *necropsy findings :* no dose related or significant effect observed
- *organ weight :*

Table 20 : organ weight (in g)

		Males				Females			
Dose level (in mg/kg bw/d)		0	100	300	1000	0	100	300	1000
Nb examined		20	20	19	18				
FBW		346.7	351.35	338.11	322.33*	215.15	223.30	215.80	217.78
Adrenals	Abs	0.0641	0.0633	0.0656	0.0574*	0.0768	0.0838	0.0803	0.0768
	Rela	0.0185	0.0181	0.0194	0.0179	0.0357	0.0376	0.0372	0.0352
Brain	Abs	2.056	2.055	2.044	2.001	1.918	1.907	1.919	1.915
	Rela	0.595	0.588	0.611	0.624	0.893	0.857	0.891	0.881
Heart	Abs	1.060	1.036	1.031	0.955**	0.740	0.763	0.739	0.749
	Rela	0.306	0.295	0.305	0.297	0.344	0.342	0.432	0.344
Kidneys	Abs	2.374	2.385	2.336	2.220	1.552	1.592	1.528	1.561
	Rela	0.684	0.680	0.691	0.688	0.721	0.713	0.708	0.717
Liver	Abs	11.805	11.499	10.775*	10.692*	7.468	7.400	7.081	7.204
	Rela	3.404	3.270	3.182**	3.311	3.465	3.317	3.278	3.311
Pituitary gland	Abs	0.0079	0.0082	0.0083	0.0073	0.0112	0.0108	0.0107	0.0199
	Rela	0.0023	0.0023	0.0025	0.0023	0.0052	0.0048	0.0050	0.0087
Spleen	Abs	0.751	0.721	0.740	0.684	0.564	0.619	0.541	0.545

	Rela	0.217	0.205	0.219	0.213	0.261	0.278	0.251	0.250
Thymus	Abs	0.481	0.468	0.490	0.452	0.438	0.426	0.441	0.418
	Rela	23.368	22.860	24.027	22.539	0.204	0.191	0.204	0.192
Thyroid/parathyroid	Abs	0.0299	0.0329	0.0344	0.0335	0.0246	0.0233	0.0233	0.0267
	Rela	0.0087	0.0090	0.0069	0.0096	0.0114	0.0104	0.0108	0.0122
Epididymides L.	Abs	0.649	0.609	0.646	0.590				
	Rela	0.187	0.173	0.193	0.183				
Epididymides R.	Abs	0.651	0.603	0.646	0.595				
	Rela	0.188	0.172	0.192	0.184				
Prostate	Abs	1.843	1.745	1.896	1.729				
	Rela	0.531	0.498	0.562	0.538				
Testis L.	Abs	1.737	1.761	1.751	1.652				
	Rela	0.5020	0.5025	0.5215	0.5112				
Testis R.	Abs	1.702	1.699	1.719	1.604				
	Rela	0.491	0.485	0.512	0.497				
Ovaries	Abs					0.130	0.123	0.115	0.112
	Rela					0.0602	0.0554	0.0536	0.0517
Uterus with cervix	Abs					0.767	0.8786	0.7195	0.8626
	Rela					0.3582	0.3970	0.3334	0.3992

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

- *histopathological findings :* no treatment related effects

For cohort 1B (F1) :

- *number of animals at the start of the test :* 20/sex/dose
- *time of death during the study and whether animals survived to termination :* in males, 1 male in control group and 1 male in the mid dose group were found dead. In female, only one female was found dead (in control group).
- *clinical observations:* all males of the highest dose exhibited moving the bedding. In females, moving the bedding was observed in 1, 6 and 20 females, respectively at 100, 300 and 1000 mg/kg bw/d.
- *body weight data :*

Table 21 : body weight (in g)

		Males				Females			
Dose level (in mg/kg bw/d)		0	100	300	1000	0	100	300	1000
In-life period for	D1	56.2	53.3	53.6	53.8	52.6	52.3	49.7	52.6

males and premating period for females	D29	221.2	222.8	222.9	222.9	160.2	160.2	161.1	163.0
	D57	315.9	312.2	324.6	321.1	203.6	204.1	207.2	214.2
	D71	344.1	339.6	351.4	343.8	213.6	218.2	223.4	226.0
	D92	376.3	368.2	374.8	372.4				
	D120	406.3	404.6	415.3	405.8				
Gestation	D0					217.41	220.37	226.88	227.18
	D7					233.65	238.10	242.24	247.94
	D14					254.00	258.70	266.12	271.81*
	D20					312.71	321.95	330.00	342.38**
Lactation	D0					241.33	242.80	253.00	262.53**
	D7					265.72	272.30	276.39	286.53**
	D14					280.83	287.35	294.28	303.16**
	D21					269.33	269.85	278.61	286.37**

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

- *food consumption :* no significant change
- *haematological and clinical biochemistry findings if available*
- *balano-preputial separation and vaginal opening :*
    - balano-separation separation : 31.90, 31.75, 32.10 and 32.00 PND, respectively at 0, 100, 300 and 1000 mg/kg bw/d (mean bw on the day of balano-separation separation : 115.50, 109.90, 113.55 and 113.65 g, respectively at 0, 100, 300 and 1000 mg/kg bw/d)
    - vaginal opening : 30.00, 31.30, 31.00 and 31.30 PND, respectively at 0, 100, 300 and 1000 mg/kg bw/d (mean bw on the day of vaginal opening : 92.05, 97.80, 95.00 and 96.75 g, respectively at 0, 100, 300 and 1000 mg/kg bw/d)
- *effects on sperm :* not examined
- *number females cycling normally and cycle length :* no information available
- *precoital interval (number of days until mating and number of oestrous periods until mating) :* 1.94, 2.20, 2.74 and 2.83 days, respectively at 0, 100, 300 and 1000 mg/kg bw/d
- *number of implantations, corpora lutea :* number examined : 19, 20, 18 and 19, respectively at 0, 100, 300 and 1000 mg/kg bw/d
    - mean nb of corpora lutea : 10.37, 11.55, 12.17 and 12.42, respectively at 0, 100, 300 and 1000 mg/kg bw/d
    - mean nb of implantation sites : 10.32, 11.05, 10.94 and 12.11, respectively at 0, 100, 300 and 1000 mg/kg bw/d
- *number of pre- and post-implantation loss :* number examined : 19, 20, 18 and 19, respectively at 0, 100, 300 and 1000 mg/kg bw/d

- mean % of pre-implantation loss : 0.38, 3.45, 8.90 and 2.50 %, respectively at 0, 100, 300 and 1000 mg/kg bw/d
- mean % of post-implantation loss : 9.05, 4.11, 4.90 and 7.61 %, respectively at 0, 100, 300 and 1000 mg/kg bw/

- *duration of gestation (calculated from day 0 of pregnancy) :* 22.29, 22.40, 22.35 and 22.24 days, respectively at 0, 100, 300 and 1000 mg/kg bw/d
- *mean live births index* : 90.95, 95.89, 95.10 and 92.39 %, respectively at 0, 100, 300 and 1000 mg/kg bw/d (number examined : 19, 20, 18 and 19, respectively at 0, 100, 300 and 1000 mg/kg bw/d)
- *necropsy findings : no treatment related effects*
- *organ weight :*

Table 22 : organ weight (in g)

		Males				Females			
Dose level (in mg/kg bw/d)		0	100	300	1000	0	100	300	1000
Nb examined		19	20	19	20	19	20	20	20
FBW		407.47	406.90	416.37	406.35	269.89	269.85	275.00	284.05
Adrenal glands	Abs	0.0514	0.0528	0.0521	0.0493	0.090	0.0862	0.0947	0.0928
	Rela	0.0127	0.0130	0.0125	0.0122	0.0334	0.0320	0.0344	0.0328
Pituitary gland	Abs	0.0084	0.0084	0.0089 (n=18)	0.0082 (n=19)	0.0192	0.0109	0.0117	0.0103
	Rela	0.0021	0.0021	0.0021	0.0020	0.0068	0.0040	0.0043	0.0037
Thyroid/ parathyroid	Abs	0.0287	0.0297	0.0279	0.0263	0.0239	0.0226	0.00229	0.0229
	Rela	0.0071	0.0073	0.0067	0.0065	0.0089	0.0084	0.0083	0.0081
Testis R.	Abs	1.8392	1.8653	1.8812	1.9260				
	Rela	0.4518	0.4622	0.4561	0.4769				
Testis L.	Abs	1.848	1.887	1.868	1.922				
	Rela	0.454	0.466	0.452	0.475				
Epididymis R.	Abs	0.6645	0.6712	0.7035	0.7220				
	Rela	0.4630	0.4663	0.1709	0.1785				
Epididymis L.	Abs	0.6568	0.6879	0.7062	0.7164				
	Rela	0.1615	0.1701	0.17191	0.1771				
Prostate	Abs	2.4757	2.6572	2.6460	2.6512				
	Rela	0.6049	0.6563	0.6419	0.6565				
Ovaries	Abs					0.1161	0.1061	0.1116	0.1159
	Rela					0.0430	0.0393	0.0411	0.0411

Uterus with cervix	Abs					0.7099	0.8521	0.6910	0.7649
	Rela					0.2632	0.3162	0.2513	0.2697

- *histopathological findings :* no treatment related effects

For F2 pups/litters of the cohort 1B:

- *mean number of pups at PND 0 (alive and dead) :*

Table 23 : number of pups

Dose level (in mg/kg bw/d)	0	100	300	1000
Tot nb of pups	9.32	10.75	10.61	11.37
Nb of males	5.11	5.40	4.83	6.16
Nb of females	4.21	5.35	5.78	5.21

- *mean still births :* 0.05, 0.15, 0.06 and 0.21, respectively at 0, 100, 300 and 1000 mg/kg bw/d
- *runts :* 0.00 in all dose groups
- *mean number of live pups (litter size) :*

Table 24 : mean number of live pups

Dose level (in mg/kg bw/d)	0	100	300	1000
PND 0	9.26	10.60	10.56	11.16
PND 4 (before interim sacrifice)	9.26	10.55	10.50	11.11
Alive pups after interim sacrifice	8.21	9.55	9.33	10.05
PND 7	8.21	9.50	9.33	10.05
PND 14	8.16	9.50	9.33	10.05
PND 21	8.11	9.50	9.33	10.05

- *mean live birth index :* 90.95, 95.89, 95.10, 92.39 %, respectively at 0, 100, 300 and 1000 mg/kg bw/d
- *sex ratio (m/f) (alive and dead) :*

Table 25 : Sex ratio

Dose level (in mg/kg bw/d)	0	100	300	1000
PND 0	1.42	1.24	0.99	1.47
PND 4	1.40	1.20	1.00	1.48
PND 7	1.55	1.32	1.12	1.51
PND 14	1.54	1.32	1.12	1.51
PND 21	1.54	1.32	1.12	1.51

- *viability index (pups surviving 4 days/total births) :* 100.00, 99.58, 99.54 and 99.54 %, respectively at 0, 100, 300 and 1000 mg/kg bw/
- *survival index :*
    - PND 4 (after interim sacrifice) – PND 14 : 99.54, 99.55, 100.00 and 100.00 %, respectively at 0, 100, 300 and 1000 mg/kg bw/d
    - PND 14 – PND 21 : 99.49, 100.00, 100.00 and 100.00 %, respectively at 0, 100, 300 and 1000 mg/kg bw/d
- *Mortality :*
    - PND 0 – 4 : 0.00, 0.42, 0.46 and 0.46 %, respectively at 0, 100, 300 and 1000 mg/kg bw/d
    - PND 4 – 21 : 0.97, 0.45, 0.00 and 0.00 %, respectively at 0, 100, 300 and 1000 mg/kg bw/d
- *mean pup weight :*

Table 26 : mean pup weight (in g)

Dose level (in mg/kg bw/d)	0	100	300	1000
Nb examined	18	20	18	18[A]
PND 0	6.26	6.39	6.36	6.11
PND 4	11.33	11.33	11.39	10.94
PND 7	16.86	16.72	16.97	16.30
PND 14	31.38	30.27	31.13	29.93
PND 21	50.62	49.62	49.94	47.09

[A] : n = 17 at D0

- *mean litter weight :*

Table 27 : mean litter weight (in g)

Dose level (in mg/kg bw/d)		0	100	300	1000
PND 0	Total	60.86	67.16	66.55	70.43
	Male	34.09	34.17	30.87	39.75
	Female	26.77	32.99	35.68	30.68
PND 4	Total	110.99	117.47	117.14	126.36
	Male	61.46	58.34	54.33	68.12
	Female	49.53	59.13	62.81	58.24
PND 7	Total	145.44	154.89	154.01	167.86
	Male	81.53	76.27	71.04	91.31
	Female	63.92	78.62	82.97	76.56
PND 14	Total	265.48	282.80	277.53	306.66
	Male	148.06	138.64	127.20	165.18

	Female	117.42	144.16	150.33	141.47
PND 21	Total	424.28	457.09	451.58	482.74
	Male	238.29	224.04	206.14	259.17
	Female	185.98	233.06	245.44	223.57

- *anogenital distance and nipple retention :*

Table 28 : AGD and nipple retention

	Males				Females			
Dose level (in mg/kg bw/d)	0	100	300	1000	0	100	300	1000
Pup weight (g)	6.39	6.51	6.39	6.09**	6.10	6.17	6.24	5.99
AGD (mm)	2.98	2.89	2.87	2.77***	1.05	1.01	1.00	1.06
Relative AGD	1.61	1.55	1.55	1.52**	0.58	0.55	0.54	0.59
Pup nipple retention on PND 12	0.33	0.20	0.42	0.68**				

** : $p < 0.01$; *** : $p < 0.001$

- *macroscopic findings :* at PND 21, one female pup exhibited discoloured thymus (red).

Cohort 2A :

- *number of animals at the start of the test :* 10/sex/dose
- *mortality :* 1 female of the mid dose was euthanized
- *clinical signs :* 4 males and 3 females of the highest dose had increased salivation. All females exposed to 1000 mg/kg bw/d exhibited moving the bedding
- *food consumption :* no significant effect
- *body weight and body weight changes :*

Table 29 : body weight data (in g)

	Males				Females			
Dose level (in mg/kg bw/d)	0	100	300	1000	0	100	300	1000
D1	54.3	52.0	53.1	52.3	52.8	50.4	53.1	52.0
D15	140.0	138.7	139.3	138.8	123.8	118.8	122.2	123.0
D29	222.9	222.8	220.1	220.4	169.7	160.5	163.7	167.4
D50	311.8	314.0	302.8	292.5	207.8	197.1	203.8	210.7

- *food/water consumption :* no significant change
- *balano-preputial separation and vaginal opening :*

- *balano-preputial separation :* 33.60, 33.80, 34.10 and 37.70 PND, respectively at 0, 100, 300 and 1000 mg/kg bw/d (bw on the day of balano-preputial separation : 124.60, 124.10, 125.80 and 148.80 g, respectively at 0, 100, 300 and 1000 mg/kg bw/d)
- *vaginal opening :* 30.90, 30.40, 30.90 and 29.70 PND, respectively at 0, 100, 300 and 1000 mg/kg bw/d (bw on the day of vaginal opening : 99.00, 93.90, 94.90 and 92.30 g, respectively at 0, 100, 300 and 1000 mg/kg bw/d)

- *motor activity :*

Table 30 : motor activity (sum interval 1, 2 and 3)

	Males				Females			
Dose level (in mg/kg bw/d)	0	100	300	1000	0	100	300	1000
SM	33.50	27.50	29.70	29.20	30.20	30.10	30.33	27.70
FM	2789.10	3308.30	3865.10	3236.00	3312.70	3973.90	4487.22	4435.00
Sum SM and FM	2822.60	3335.80	3894.80	3265.20	3342.90	4004.00	4517.56	4462.70
SR	27.80	25.00	27.00	31.30	22.20	22.40	28.44	28.50
FR	145.40	139.25	148.10	140.40	128.40	113.20	144.56	122.60
Sum SR and FR	173.20	164.25	175.10	171.70	150.60	135.60	173.00	151.10

- *mean max auditory startle response at PND 24 :* 0.664, 0.573, 0.613 and 0.690 in males and 0.683, 0.582, 0.622 and 0.666 in females, respectively at 0, 100, 300 and 1000 mg/kg bw/d
- *gross pathology findings:* only one female of the mid dose group exhibited a uterus's dilatation. No other findings observed
- *organ weight :*

Table 31 : organ weight (in g)

		Males				Females			
Dose level (in mg/kg bw/d)		0	100	300	1000	0	100	300	1000
FBW		326.30	330.90	315.20	303.60	212.60	201.90	207.22	211.00
brain	Abs	1.9705	1.9155	1.9295	1.9442	1.8621	1.8046	1.8637	1.8052
	Rela	0.6052	0.5811	0.6147	0.6426	0.8766	0.8972	0.9002	0.8599

- *histopathology findings:* 1 female exposed to 1000 mg/kg bw/d had single fiber degenerative of sciatic nerve. This effect was also observed in 2 males and 1 female of the control group.

Cohort 2B

- *body weight and body weight changes :* not examined
- *description, severity, time of onset and duration of clinical signs:* not examined

- *haematological findings:* not examined
- *clinical biochemistry findings:* not examined
- *gross pathology findings:* no change observed
- *organ weight :*

Table 32 : organ weight data (in g)

		Males				Females			
Dose level (in mg/kg bw/d)		0	100	300	1000	0	100	300	1000
Nb examined		10	10	10	10	10	10	10	10
FBW		52.3	48.1	47.8	49.5	50.1	47.0	50.3	48.4
Brain	Abs	1.523	1.490	1.528	1.509	1.491	1.425	1.429	1.463
	Rela	2.941	3.128	3.233	3.060	2.994	3.085	2.856	3.038

- *histopathology findings:* not examined

Cohort 3 :

- *mortality and time to death :* 1 female of the low dose group, 1 male of the mid dose group and 1 male of the highest dose group were found dead
- *description, severity, time of onset and duration of clinical signs :* excessive salivation was noted in 2 males and 1 female of the highest dose and all male and 7 females of this group exhibited central nervous system symptom (moving the bedding)
- *body weight and body weight changes :*

Table 33 : body weight data (in g)

	Males					Female				
Dose level (in mg/kg bw/d)	0	100	300	1000	PC	0	100	300	1000	PC
D1	54.4	54.2	52.3	53.1	53.1	53.8	51.9	49.0	48.7	52.2
D15	145.0	152.5	139.2	139.0	137.3	125.3	123.2	121.7	120.8	124.2
D29	219.6	212.5	225.6	220.4	226.0	163.7	166.1	164.2	163.7	164.9
D43	275.1	294.7	287.4	276.3	262.4	190.9	187.2	190.2	186.8	176.3

- *food consumption :* no effects observed
- *balano-preputial separation :* 31.00, 32.10, 31.10, 33.10 and 32.60 PND, respectively at 0, PC, 100, 300 and 1000 mg/kg bw/d (bw on the day of balano-preputial separation was of 105.1, 117.9, 109.8, 121.4, 115.6 g, respectively at 0, PC, 100, 300 and 1000 mg/kg bw/d)

- *vaginal opening :* 30.90, 31.8, 30.8, 33.0, 30.8 PND, respectively at 0, PC, 100, 300 and 1000 mg/kg bw/d (bw on the day of vaginal opening was of 101.9, 102.1, 97.9, 103.4 and 93.2, respectively at 0, PC, 100, 300 and 1000 mg/kg bw/d)
- *mean IgM serum levels:*

Table 34 : IgM serum level (in ng/ml)

		Males					Female				
Dose level (in mg/kg bw/d)		0	PC	100	300	1000	0	PC	100	300	1000
Anti-KLH IgM	Baseline	38306	37146	40129	33478	36858	43182	56579	59730	55998	53539
	D6	59517	45725	48187	47404	47050	52136	46821	52025	50412	51085
Total IgM	Baseline	50457	46246	53960	43916	44836	51163	44183	57456	46696	44951
	D6	85678	32436	65536	58650	61502	67790	37980	84141	80677	68915

- *mean IgG serum levels :*

Table 35 : IgG serum level (in ng/ml)

		Males					Female				
Dose level (in mg/kg bw/d)		0	PC	100	300	1000	0	PC	100	300	1000
Total IgG	Baseline	528458	475848	558915	472083	470908	744238	693940	859372	685535	587781
	D6	866785	569692	898070	713330	924306	1173465	714770	1610619	1209063	1183008

Anti-KLH IgG was below level of quantification

- *haematological findings:* not examined
- *clinical biochemistry findings:* not examined
- *gross pathology findings:* no treatment related effect observed
- *histopathology findings:* not examined

Cohort 4 :

- *number of animals at the start of the test :* 10 males and 10 females in control and high dose
- *mortality and time to death :* no mortality observed
- *description, severity, time of onset and duration of clinical signs :* all males and 2 females exposed to 1000 mg/kg bw/d had central nervous system symptoms (moving bedding). And 5 females exhibited excessive salivation.
- *body weight and body weight changes :*

Table 36 : body weight data (in g)

	Male		Female	
Dose level (in mg/kg bw/d)	0	1000	0	1000
Nb examined	10	10	10	10
D1	54.40	52.90	50.00	47.10
D8	89.80	91.70	82.30	79.00
D15	136.80	136.10	114.50	113.00

- *food consumption :* no effect observed
- *mean escape latency :*

Table 37 : mean escape latency during learning and memory phase (in seconds)

	Male		Female	
Dose level (in mg/kg bw/d)	0	1000	0	1000
During learning phase (PND 28/29)	7.50 ± 4.89	9.21 ± 2.31	10.76 ± 3.80	8.65 ± 4.81
During memory phase (PND 35/36)	8.02 ± 3.41	6.95 ± 0.91	8.63 ± 0.86	6.07 ± 1.37*

* : $p < 0.05$

- *haematological findings:* not examined
- *clinical biochemistry findings:* not examined
- *gross pathology findings:* no effect observed
- *histopathology findings:* not examined

3.10.1.2 Dose range finding study for reproduction/developmental toxicity screening test (Anonymous, 2018)

Study reference:

Anonymous, 2018

Detailed study summary and results:

Test type

OECD TG 421

GLP

Aim of this study : generate toxicological information on the maximum tolerated dose of propylparaben to select dose levels for scheduled EOGRTS study.

Test substance

- Propylparaben
- *Degree of purity :* 99.7 %

Test animals

- *Species/strain/sex :* rat / Wistar / both sexes
- *No. of animals per sex per dose :* 5/sex for control group and 10/sex for each treated groups
- *Age and weight at the study initiation :* 8 to 9 weeks old (at the start of the treatment period), 236 to 284 g for males and 155 to 188 g for females (at the allocation of the animals to the groups)

Administration/exposure

- *Route of administration :* oral, gavage
- *duration and frequency of test/exposure period :* min. 35 days for males (21 days of premating and max 14 days of mating). Females were exposed during 21 days of pre-mating and up to 14 days of mating. One dam of each treated group was dosed up to GD 20, the other dams were dosed during gestation and up to PND 21. The surviving pups of one litter from each group were treated from PND 13 to PND 21. Daily
- *doses/concentration levels, rationale for dose level selection :* 0, 500 and 1000 mg/kg bw/d
- *vehicle:* hydroxyethyl-cellulose mittelviskos, 1%

Results and discussion

For P (per dose):

- *number of animals at the start of the test :* 5/sex in control group and 10/sex at 500 and 1000 mg/kg bw/d
- *time of death during the study and whether animals survived to termination :* one male of the low dose was found dead on PMD 8. One female exposed to 1000 mg/kg bw/d was found dead on PND 5 (gavage error).
- *clinical observations :* females of all doses exhibited alopecia on different locations at different periods of the study period. Males of the highest dose exhibited also alopecia but from premating day 6.
- *body weight data :*

Table 38 : body weight data (in g)

		Males			Females		
Dose level (in mg/kg bw/d)		0	500	1000	0	500	1000
Nb examined		5	10	10	5	10	10
Premating period	D1	272.40	271.40	269.20	182.80	173.60	174.80
	D14	362.20	323.00[A]	321.00	206.20	195.80	196.00
	D21	340.40	343.67 [A]	337.20	212.00	205.00	205.20
Mating and post mating period	D7	343.80	354.22 [A]	350.20			
	D14	364.20	373.33 [A]	371.20			
Gestation period	D0				219.80	210.22 [A]	210.40

	D14				267.60	266.20	263.56 [A]
	D20				331.20	337.90	333.20
Lactation period	D0				241.75[B]	252.33[A]	251.00[A]
	D9				280.25 [B]	271.67[A]	276.50[C]
	D21				273.00 [B]	284.00[A]	274.75[C]

[A] : Nb examined = 9 ; [B] : nb examined = 4 ; [C] : nb examined = 8

- *haematological and clinical biochemistry findings if available :* not examined
- *effects on sperm :* not examined
- *number of P and F1 females cycling normally and cycle length :* not examined
- *precoital interval (number of days until mating and number of oestrous periods until mating)* : 7.20, 3.00 and 2.30 days, respectively at 0, 500 and 1000 mg/kg bw/d (n : 5, 10 and 10, respectively at 0, 500 and 1000 mg/kg bw/d)
- *duration of gestation (calculated from day 0 of pregnancy) :* 22.25, 22.33 and 22.11 days, respectively at 0, 500 and 1000 mg/kg bw/d (n : 4, 9 and 9, respectively at 0, 500 and 1000 mg/kg bw/d)
- *number of corpora lutea :* 14.00, 13.00 and 14.00, respectively at 0, 500 and 1000 mg/kg bw/d (N : 1 for all groups)

  13.75, 13.22 and 13.63, respectively at 0, 500 and 1000 mg/kg bw/d (N : 4, 9 and 8, respectively at 0, 500 and 1000 mg/kg bw/d)
- *number of implantations :* 12.00, 11.00 and 14.00, respectively at 0, 500 and 1000 mg/kg bw/d (N : 1 for all groups)

  13.75, 13.11 and 13.38, respectively at 0, 500 and 1000 mg/kg bw/d (N : 4, 9 and 8, respectively at 0, 500 and 1000 mg/kg bw/d)
- *number of pre- and post-implantation loss :* N : 4, 9 and 8, respectively at 0, 500 and 1000 mg/kg bw/d :
  - pre- : 0.00, 0.79 and 1.74, respectively at 0, 500 and 1000 mg/kg bw/d
  - post- : 6.47, 6.74 and 8.72, respectively at 0, 500 and 1000 mg/kg bw/d
- *resorptions :* early resorptions : 0.0, 0.0 and 2.0, respectively at 0, 500 and 1000 mg/kg bw/d. No late resorptions observed (N : 1 for all groups).
- *number of dams with abortions, early deliveries, stillbirths, resorptions and/or dead foetuses :*

Table 39 : litter data at PND 0

Dose level (in mg/kg bw/d)	0	500	1000
Nb examined	4	9	9
Tot. nb of pups	12.75	12.44	12.56

Mean nb of live pups	12.75	12.22	12.22
Mean nb of still birth	0.00	0.11	0.22
Mean nb of runts	0.00	0.11	0.11

- *necropsy findings :* 1 female at 500 mg/kg bw/d exhibited fluid filled uterus and 1 female of the highest dose exhibited dark lung
- *histopathological findings:* animal with fluid filled uterus had an uterus horn dilatation and female with dark lung showed congestion and atelactasis
- *body weight change and gravid uterine weight, including optionally, body weight change corrected for gravid uterine weight :*

Table 40 : gravid uterus weight (in g)

Dose level (in mg/kg bw/d)	0	500	1000
At GD 20			
Nb examined	1	1	1
FBW	340.00	321.00	358.00
Uterus weight	62.80	65.80	70.00
Adjusted maternal weight	277.20	255.20	288.00

For pups/litters (per dose):

- *mean total number of pups at PND 0 :* 12.75, 12.44, 12.56, respectively at 0, 500 and 1000 mg/kg bw/d (N : 4, 9 and 9, respectively at 0, 500 and 1000 mg/kg bw/d)
- *mean number of live pups (litter size) at PND 0:* 12.75, 12.22, 12.22, respectively at 0, 500 and 1000 mg/kg bw/d (mean number of still birth : 0.00, 0.11 and 0.22, respectively at 0, 500 and 1000 mg/kg bw/d ; mean number of runt : 0.0, 0.11 and 0.11, respectively at 0, 500 and 1000 mg/kg bw/d) (N : 4, 9 and 9, respectively at 0, 500 and 1000 mg/kg bw/d)
- *mean number of live pups at PND 4:* 12.75, 12.00 and 11.22, respectively at 0, 500 and 1000 mg/kg bw/d (N : 4, 9 and 9, respectively at 0, 500 and 1000 mg/kg bw/d)
- *sex ratio at D0 :* 0.84, 1.21 and 1.01 males/females, respectively at 0, 500 and 1000 mg/kg bw/d
- *viability index :* N : 4, 9 and 8, respectively at 0, 500 and 1000 mg/kg bw/d
    - PND 0-4 : 100.0, 98.29 and 96.64 %, respectively at 0, 500 and 1000 mg/kg bw/d
    - PND 4-13 : 100.0, 100.0 and 100.0 %, respectively at 0, 500 and 1000 mg/kg bw/d
    - PND 13-21 : 100.0, 100.0 and 98.61 %, respectively at 0, 500 and 1000 mg/kg bw/d
- *Mean max startle reflex measuring PND 25 :* 0.73 and 0.66 in females and 0.79 and 0.62 in males, respectively at 0 and 1000 mg/kg bw/d
- *mean pup bw and litter weight :*

Table 41 : mean pup bw (in g)

	Pup bw			Litter weight		
Dose level (in mg/kg bw/d)	0	500	1000	0	500	1000
Nb examined	4	9	9	4	9	9
D0	5.84	6.39	5.86	74.33	77.82	71.67
D4	10.23	10.82	10.19	130.10	125.68	113.78
D7	25.48	25.58	25.50	294.40	275.48	265.09
D13-14	33.35	33.05	30.55	342.98	312.44	284.06
D21	45.45	44.53	42.12	467.70	422.61	373.57

- *external, soft tissue and skeletal malformations and other relevant alterations :* no relevant external gross abnormalities observed

3.10.1.3 Combined repeated dose toxicity study 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

- Propylparaben
- *Degree of purity :* 99.7 %

Test animals

- *Species/strain/sex :* Rat / Wistar / Both sexes
- *No. of animals per sex per dose :* 11 animals/sex/group
- *Age and weight at the study initiation :* 11 weeks, 344 to 381 g for males and 184 to 209 g for females

Administration/exposure

- *Route of administration* : oral (feed)
- *duration and frequency of test/exposure period :*
    - Males : min. 4 weeks (14 days of pre-mating period and 14 days of pairing period) (necropsy after treatment of at least 28 days)

- Females : approx. 7 weeks (14 days of pre-mating period, maximum 14 days of pairing period, gestation period (21 days) et until days 3 of lactation) (necropsy of females and pups on DPP 4)

- *doses/concentration levels :* 0, 1500, 4500 and 15000 ppm

Table 42 : Mean achieved dose level (mg/kg bw/d)

	Males		Females		
	Pre-pairing period	After pairing period	Pre-pairing period	Gestation period	Lactation period
0 ppm	0	0	0	0	0
1500 ppm	98.0	59.3	16.0	121.6	137.3
4500 ppm	305.1	178.3	341.9	349.2	431.8
15000 ppm	980.9	605.0	1076.4	1124.6	1380.0

- *vehicle :* not specified

Description of test design:

- *details on mating procedure (M/F ratios per cage, length of cohabitation, proof of pregnancy) :* females were housed with sexually mature males (1:1) until evidence of copulation.
- *premating exposure period for males and females :* 14 days
- *oestrous cycle length and pattern, sperm examination, clinical observations performed and frequency*
  - *Oestrous cycles :* from day 1 of the pre-mating period until the day 0 of post mating
  - *Sperm analysis :* 5 males per group were examined
- *necropsy :* after treatment of at least 28 days for males and at day 4 post partum for females and pups.

Results and discussion

For P (per dose):

- *time of death during the study and whether animals survived to termination :* all animals survived during the study period.
- *clinical observations:* at 1500 ppm, one female exhibited malpositioned hind leg during the gestation period. No other abnormalities were recorded.
- *food consumption :* no effects observed

Table 43 : Mean food consumption (g/animal/day)

	Males				Females			
Dose level (in ppm)	0	1500	4500	15000	0	1500	4500	15000
Pre-pairing period	24.8	24.8	26.0	24.5	14.9	15.5	15.4	14.2
After-pairing period	25.4	25.2	25.7	25.0	/	/	/	/
Gestation period	/	/	/	/	19.5	20.6	19.7	18.4

Lactation period	/	/	/	/	26.5	22.4	23.1	21.7

Stat : Dunnett-test

- *body weight data for P animals :*
  - Males : no significant changes observed in absolute body weight

Table 44 : Mean body weight in males (in g)

Dose level (in ppm)		0	1500	4500	15000
Pre-pairing period	D1	356	355	358	355
	D7	378	379	381	372
	D14	386	386	393	380
Pairing period	D1	389	394	398	386
	D8	407	408	411	397
After-pairing period	D1	410	411	415	401
	D6	424	425	430	415
	D11	439	440	446	430

Stat : Dunnett-test

  - Females : no significant changes observed in absolute body weight

Table 45 : Mean body weight in females (in g)

Dose level (in ppm)		0	1500	4500	15000
Pre-pairing period	D1	196	193	193	195
	D7	199	199	201	197
	D14	201	202	202	197
Gestation period	D1	208	209	211	203
	D7	226	231	232	224
	D14	255	258	260	248
	D21	319	317	323	304
Lactation period	D1	236	237	234	230
	D4	249	248	244	234

Stat : Dunnett-test

- *FOB :* no treatment-related effects observed

Table 46 : FOB data

	Males (after pairing period)				Females (during lactation period)			
Dose level (in ppm)	0	1500	4500	15000	0	1500	4500	15000
Grip strength								
Mean grip force (Kg)	0.44	0.38	0.43	0.38	0.33	0.31	0.28	0.27

Mean grip hind (Kg)	0.34	0.30	0.31	0.33	0.20	0.21	0.21	0.19
Body temperature								
Mean degrees (C)	38.5	38.1	38.1	38.0*	38.4	38.3	38.2	38.1

Stat : Dunnett-test ; * : $p < 0.05$
Males : shortly before sacrifice ; Females : 3 DPP (day post-partum)

- *locomotor activity :* no effect observed

Table 47 : Mean beam counts during the 30 min of measurement

	Males (after pairing period)				Females (during lactation period)			
Dose level (in ppm)	0	1500	4500	15000	0	1500	4500	15000
Mean beam counts	1452	1262	1347	1214	586	787	692	519

Stat : Steel-test

- *haematological findings :* no treatment-related effects observed

Table 48 : haematological data in males on day 14

	RBC (T/l) [A]	Hg (mmol/l) [A]	Ht (rel. l) [A]	MCV (fl) [A]	RDW (rel. l) [A]	MCH (fmol) [A]	MCHC (mmol/l) [A]
0 ppm	8.47	9.8	0.45	52.8	0.126	1.16	22.00
1500 ppm	8.50	9.7	0.45	52.7	0.116	1.15	21.72
4500 ppm	8.55	9.8	0.45	52.3	0.121	1.15	21.89
15000 ppm	8.58	10.0	0.45	52.5	0.115*	1.1	22.22
	HDW (mmol/l) [A]	WBC (G/l) [A]	Neut (G/l) [AB]	Eos (G/l) [AB]	Baso (G/l) [AB]	Lymph (G/l) [AB]	Mono (G/l) [AB]
0 ppm	1.87	8.29	1.00	0.07	0.06	6.84	0.19
1500 ppm	1.71	7.49	0.98	0.09	0.09	5.98	0.19
4500 ppm	1.80	7.46	1.05	0.11*	0.06	5.92	0.20
15000 ppm	1.78	8.92	1.12	0.10	0.08	7.25	0.22

	Plt (G/l) [A]	PT (rel. l) [B]	PTT (sec) [B]
0 ppm	1051	0.81	23.0
1500 ppm	1016	0.84	23.3
4500 ppm	1069	0.81	22.9
15000 ppm	1019	0.83	23.2

Stat : Dunnett-test (A) and Steel-test (B) ; * : $p < 0.05$

Table 49 : haematological data in females on day 14

	RBC (T/l) [A]	Hg (mmol/l) [A]	Ht (rel. l) [A]	MCV (fl) [A]	RDW (rel. l) [A]	MCH (fmol) [A]	MCHC (mmol/l) [A]
0 ppm	7.98	9.4	0.42	53.3	0.112	1.18	22.05

1500 ppm	8.04	9.4	0.42	52.8	0.112	1.17	22.16
4500 ppm	7.63	9.0	0.41	54.4	0.116	1.18	22.68
15000 ppm	7.72	9.2	0.41	53.7	0.117	1.19	22.09
	HDW (mmol/l) [A]	WBC (G/l) [A]	Neut (G/l) [AB]	Eos (G/l) [AB]	Baso (G/l) [AB]	Lymph (G/l) [AB]	Mono (G/l) [AB]
0 ppm	1.45	5.20	0.76	0.06	0.04	4.15	0.10
1500 ppm	1.47	5.44	0.57	0.07	0.04	4.59	0.09
4500 ppm	1.44	5.64	0.59	0.06	0.04	4.74	0.11
15000 ppm	1.48	5.78	0.64	0.06	0.04	4.85	0.11

	Plt (G/l) [A]	PT (rel. l) [B]	PTT (sec) [B]
0 ppm	1136	0.78	28.9
1500 ppm	1031	0.81	31.3
4500 ppm	992	0.82	32.0
15000 ppm	1177	0.81	30.2

Stat : Dunnett-test (A) and Steel-test (B) ; * : $p < 0.05$

- *clinical biochemistry findings :* triglycerides value was significantly higher at the highest dose compared to control group.

Table 50 : Biochemistry data in males

	Glucose (mmol/l)	Urea (mmol/l)	Creat (µmol/l)	Bili-t (µmol/l)	Bile ac (µmol/l)	Chol (mmol/l)	Trigl (mmol/l)
0 ppm	6.10	4.82	19.2	2.02	37.22	2.35	0.71
1500 ppm	5.62	4.61	22.2*	1.73	35.22	2.33	0.90
4500 ppm	5.56	5.53	24.2**	2.07	31.98	2.72	0.97
15000 ppm	6.38	5.37	22.0	1.88	43006	2.75	1.03*
	Asat (U/l)	Alat (U/l)	ALP (U/l)	GGT (U/l)	Na (mmol/l)	K (mmol/l)	Cl (mmol/l)
0 ppm	60.4	25.1	92.9	0.0	145.4	4.03	100.7
1500 ppm	54.5	15.8*	83.8	0.0	146.2	4.07	101.5
4500 ppm	69.3	22.7	80.2	0.0	146.6	4.09	102.3
15000 ppm	62.0	18.5	68.0	0.0	145.2	4.30	100.3

	Ca (mmol/l)	P (mmol/l)	Prot (g/l)	Alb (g/l)	Glob (g/l)	A/G ratio
0 ppm	2.79	2.18	66.10	44.08	22.02	2.00
1500 ppm	2.77	2.21	65.60	42.73	22.87	1.88
4500 ppm	2.80	2.39	66.03	44.30	21.73	2.01
15000 ppm	2.84	2.30	67.65	44.84	22.81	1.91

Stat : Dunnett-test (except for GGT and A/G ratio : Steel-test)
* : $p < 0.05$; ** : $p < 0.01$

Table 51 : Biochemistry data in females

	Glucose (mmol/l)	Urea (mmol/l)	Creat (µmol/l)	Bili-t (µmol/l)	Bile ac (µmol/l)	Chol (mmol/l)	Trigl (mmol/l)
0 ppm	7.42	6.36	24.9	1.73	12.58	1.93	0.50
1500 ppm	6.78	6.72	25.9	2.16	13.98	1.91	0.41
4500 ppm	7.28	6.85	27.2	1.88	24.00	1.64	0.50
15000 ppm	8.04	5.84	23.9	1.99	26.04	1.95	0.46
	Asat (U/l)	Alat (U/l)	ALP (U/l)	GGT (U/l)	Na (mmol/l)	K (mmol/l)	Cl (mmol/l)
0 ppm	64.8	24.4	43.2	0.0	145.6	3.85	103.9
1500 ppm	68.0	25.8	43.2	0.0	144.0	3.67	102.6
4500 ppm	65.8	20.9	43.1	0.0	145.8	3.93	103.5
15000 ppm	65.6	21.3	42.9	0.0	145.8	3.80	103.9
	Ca (mmol/l)	P (mmol/l)	Prot (g/l)	Alb (g/l)	Glob (g/l)	A/G ratio	
0 ppm	2.66	1.51	70.21	51.30	18.91	2.65	
1500 ppm	2.76	1.61	71.64	52.21	19.42	2.70	
4500 ppm	2.72	1.77	72.79	53.78	19.02	2.73	
15000 ppm	2.85	1.50	72.59	55.11	17.49	2.83	

Stat : Dunnett-test (except for GGT and A/G ratio : Steel-test)

- *effects on sperm :*

Table 52 : Sperm analysis

Dose level (in ppm)	0	1500	4500	15000
Nb examined	5	5	5	5
Mean % progressive	84.2	85.5	83.6	86.9
Mean % stationary	2.4	2.3	2.5	3.0
Mean % not motile	13.4	12.2	13.9	10.1
Mean testis sperm count (millions/g)	123.7	NT	NT	130.0
Mean cauda epididymis sperm count (millions/g)	707.7	NT	NT	834.0
% of normal sperm	96.4	NT	NT	97.6

Stat : Dunnett-test

- *number of P cycling normally and cycle length :* no effects observed

  Mean days between oestrous : 4.0 d in all groups

- *mean precoital interval (number of days until mating and number of oestrous periods until mating) :* 2.6, 3.3, 4.0 and 2.9 d respectively at 0, 1500, 4500 and 15000 ppm

- *fertility index :* 90.9, 90.9, 100.0 and 90.9 % respectively at 0, 1500, 4500 and 15000 ppm
- *number of implantations, corpora lutea :*
    - *Mean corpora lutea count :* 12.3, 13.2, 13.3 and 12.0 respectively at 0, 1500, 4500 and 15000 ppm
    - *Mean implantation sites :* 11.9, 10.5, 12.3 and 11.3, respectively at 0, 1500, 4500 and 15000 ppm
- *number of pre- and post-implantation loss*
    - *% of post-implantation loss :* 5.9, 6.7, 5.2 and 12.4 % respectively at 0, 1500, 4500 and 15000 ppm (litter affected : 5, 7, 5 and 7 litters ; total nb : 7, 7, 7 and 14 ; mean : 0.7, 0.7, 0.6 and 1.4) (Stat : Steel test)
    - *% of pre-implantation loss :* no information available
- *mean duration of gestation (calculated from day 0 of pregnancy) :* 21.2, 21.6, 21.2, 21.1 d, respectively at 0, 1500, 4500 and 15000 ppm
- *Mean number of living pups at first litter check :* 11.2, 9.8, 11.6 and 9.9, respectively at 0, 1500, 4500 and 15000 ppm
- *necropsy findings :*
    - Males :

      Without findings : 10, 10, 8 and 7, respectively at 0, 1500, 4500 and 15000 ppm (11 animals examined per group)

      Enlarged liver in 1 (9%), 1 (9%), 2 (18%) and 4 (36%) animals, respectively at 0, 1500, 4500 and 15000 ppm

      Pelvic dilatation in kidneys in 0, 0, 1 (9%) and 0 animals, respectively at 0, 1500, 4500 and 15000 ppm

      Focus/foci in thymus in 0, 0, 0 and 1 (9%) animals, respectively at 0, 1500, 4500 and 15000 ppm
    - Females :

      Without findings : 11, 8, 10 and 11, respectively at 0, 1500, 4500 and 15000 ppm

      Pelvic dilatation in kidney in 0, 1 (9%), 0 and 0 animals, respectively at 0, 1500, 4500 and 15000ppm

      Ovaries discoloration in 0, 0, 1 (9%) and 0 animals, respectively at 0, 1500, 4500 and 15000 ppm

      Focus/foci in thymus in 0, 2 (18%), 0 and 0 animals, respectively at 0, 1500, 4500 and 15000 ppm
- *organ weight :*

Table 53 : absolute organ weight (in g) and relative organ weight (organ/bw ratio in %)

	Males	Females

Dose level (in ppm)		0	1500	4500	15000	0	1500	4500	15000
FBW		422.2	424.5	430.7	413.4	234.2	236.4	233.9	222.0
Adrenals	Abs	0.073	0.076	0.066	0.067	0.083	0.083	0.078	0.066
	Rela	0.017	0.018	0.016	0.016	0.035	0.035	0.033	0.031
Brain	Abs	2.08	2.05	2.02	2.02	1.76	1.83	1.79	1.80
	Rela	0.50	0.48	0.47	0.48	0.76	0.77	0.77	0.82
Heart	Abs	1.04	0.98	0.99	0.95	0.70	0.74	0.75	0.69
	Rela	0.24	0.23	0.23	0.22	0.30	0.31	0.32	0.32
Kidneys	Abs	2.49	2.29**	2.35	2.34*	1.27	1.34	1.32	1.24
	Rela	0.59	0.54*	0.55*	0.55	0.54	0.56	0.56	0.57
Liver	Abs	14.25	14.57	14.94	15.37	8.48	9.13	9.16	8.17
	Rela	3.39	3.39	3.49	3.64	3.64	3.85	3.89	3.75
Spleen	Abs	0.88	0.82	0.92	0.90	0.61	0.67	0.65	0.55
	Rela	0.21	0.19	0.21	0.21	0.26	0.28	0.28	0.25
Thymus	Abs	0.385	0.374	0.366	0.407	0.199	0.177	0.195	0.166
	Rela	0.091	0.087	0.085	0.096	0.085	0.075	0.083	0.076
Epididymide L.	Abs	0.670	0.682	0.712	0.671				
	Rela	0.159	0.161	0.165	0.162				
Epididymide R.	Abs	0.642	0.638	0.705**	0.695*				
	Rela	0.152	0.150	0.164	0.168*				
Testis L.	Abs	2.05	2.09	2.15	2.09				
	Rela	0.49	0.49	0.50	0.50				
Testis R.	Abs	2.03	2.04	2.10	2.07				
	Rela	0.48	0.48	0.49	0.50				

Stat : Dunnett-test ; * : $p < 0.050$; ** : $p < 0.01$

- *histopathological findings:*

Table 54 : Microscopical findings

		Males				Females			
Dose level (in ppm)		0	1500	4500	15000	0	1500	4500	15000
Kidneys	Tubular basophilia	2/5	NT	0/1	0/5	1/5	0/1	NT	0/5
	Hyaline droplets	3/5	NT	1/1	3/5	0/5	0/1	NT	0/5
	Tubular cystic dilatation	0/5	NT	0/1	0/5	0/5	0/1	NT	1/5
	Pelvic dilatation	0/5	NT	1/	0/5	0/5	1/1	NT	0/5
Liver	Inflammatory foci	1/5	1/1	2/2	1/5	1/5	NT	NT	1/5
Thymus	Haemorrhage	0/5	NT	NT	1/5	0/5	2/2	NT	0/5

Testes	Tubular degeneration/atrophy	3/11	0/1	NT	2/11				
	Sertoli cell vacuolation	5/11	0/1	NT	5/11				
Epididymides	Cellular debris	1/11	0/1	NT	0/11				
	Mononuclear foci	7/11	0/1	NT	8/11				
Prostate	Inflammation	1/11	1/1	NT	2/11				
Ovaries	Congestion					0/11	0/1	1/1	0/11

For F1 pups/litters (per dose):

- *mean number of live pups (litter size) :*
  - Total number of living pups at first litter check : 112, 98, 128 and 99, respectively at 0, 1500, 4500 and 15000 ppm
  - Mean number of living pups at first litter check : 11.2, 9.8, 11.6 and 9.9, respectively at 0, 1500, 4500 and 15000 ppm
  - Birth index : 94.1, 93.3, 94.8 and 87.6 %, respectively at 0, 1500, 4500 and 15000 ppm
- *dead pups at first litter check :* 0 in all groups
- *sex ratio :* 45/55, 50/50, 44/56 and 51/49 % of males/females, respectively at 0, 1500, 4500 and 15000 ppm
- *viability index (pups surviving 4 days/total births) :* 100, 98.0, 99.2 and 100.0 %, respectively at 0, 1500, 4500 and 15000 ppm

  Low dose group : 1 male died at day 2 PP and 1 female died at day 4 PP

  Mid dose group : 1 female died at day 3 PP

  No mortality was observed in control and high dose groups
- *total living pups at day 4 PP :* 112, 96, 127 and 99, respectively at 0, 1500, 4500 and 15000 ppm (mean 11.2, 9.6, 11.5 and 9.9, respectively at 0, 1500, 4500 and 15000 ppm)
- *clinical signs :* no effects observed
- *mean litter or pup weight by sex and with sexes combine :*

Table 55 : mean pups body weight (in g)

Dose level (in ppm)		0	1500	4500	15000
D1	M+F	6.3	6.3	6.0	6.1
	M	6.4	6.4	6.1	6.0
	F	6.1	6.3	5.9	6.0
D4	M+F	8.7	8.9	8.1	8.5
	M	8.9	8.9	8.2	8.2
	F	8.5	9.0	8.0	8.4

Stat : Dunnett-test

- *external, soft tissue and skeletal malformations and other relevant alterations :*
    - External examination : no abnormalities observed in control and mid dose group. 2 males and 2 females of one litter in low dose group exhibited no milk in the stomach and 1 male of the highest dose had throat and chest hematoma
    - Soft tissue and skeletal malformations : not examined
- *macroscopical findings :* no findings observed

3.10.1.4 Sivaraman *et al.*, 2018

Study reference:

Sivaraman *et al.*, 2018, Safety assessment of propylparaben in juvenile rats, Regulatory Toxicology and Pharmacology, 92, 370-381.

Detailed study summary and results:

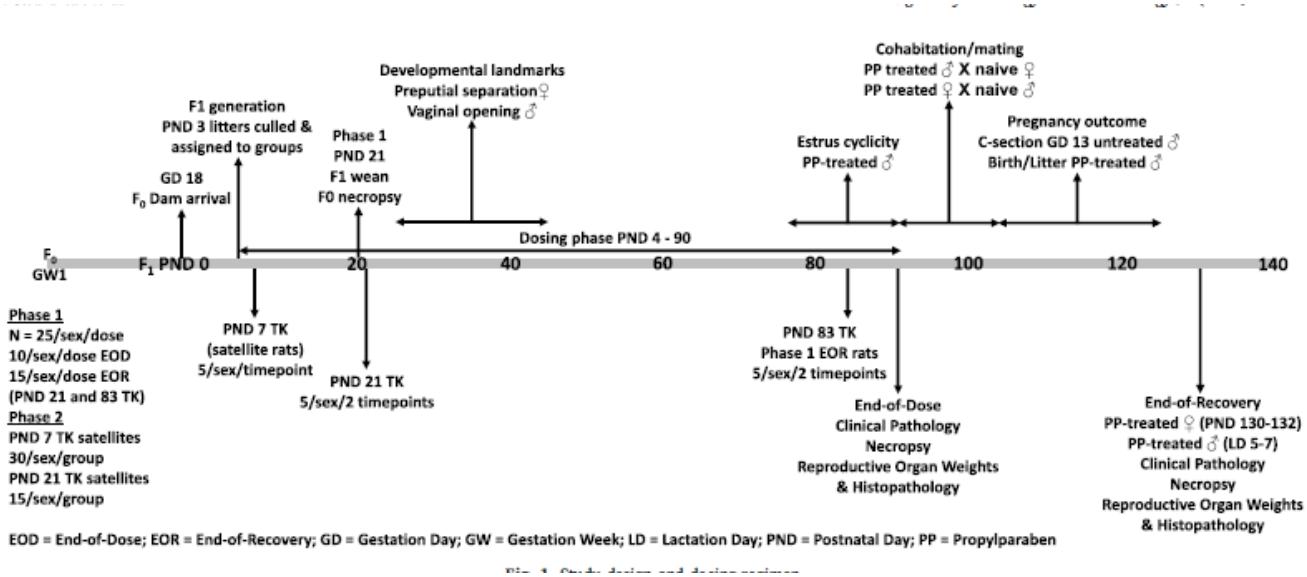
Test type

2 separate studies to assess :

- Phase 1 : Reproductive development and function in male and female rats when administered on PND 4 to PND 90
- Phase 2 : Uterus weight in immature female rats when administered on PND 4 to PND 7 or 21

Pregnant dams were used to produce the F1-generation litters which were the experimental population

Figure 2 : study design (Sivaranam *et al.*, 2018)



Test substance

- Propylparaben
- *Degree of purity :* 99.7%

Test animals

- *Species/strain/sex :* Rat / SD / both sexes

- *No. of animals per sex per dose :* Phase 1 : 25/sex/dose (10/sex/dose end-of dose necropsy subset and 15/sex/dose reproduction/recovery subset)
  Phase 2 : 15 or 30/sex/dose for toxicokinetic assessment (PND 7 or 21)
- *Age and weight at the study initiation :* Phase 1 : 8.5 to 13.6 g for males and 8.7 to 13.6 g for females
  Phase 2 : 7.8 to 15.4 g for males and 6.5 to 14.6 g for females

Administration/exposure

- *Route of administration :* oral, gavage
- *duration and frequency of test/exposure period :* phase 1 : from PND 4 through PND 90.
  Phase 2 : from PND 4 through PND 7 or from PND 4 through PND 21
- *doses/concentration levels :* 0, 10, 100 and 1000 mg/kg bw/d
- *vehicle:* 1% hydroxyethylcellulose

Results and discussion

For parental F1 (per dose) :

- *clinical observations :* at 1000 mg/kg bw/d : increased incidence of abdominal distension during pre-weaning period (PND 7 to 21) (4-5 animals/sex vs 1 male in control) + increased incidence of salivation, which was observed immediately after dosing
- *body weight data :* at 1000 mg/kg bw/d : slightly increased in males (approximately of 7% prior to weaning and prior to end-of dose necropsy compared to control groups). This change was correlated to a higher food consumption.
- *vaginal patency :* 33.9, 32.4, 32.7 and 31.2** PND (bw 128.6, 125.2, 122.1 and 115.2** g), respectively at 0, 10, 100 and 1000 mg/kg bw/d
- *preputial separation :* 42.1, 42.3, 42.3 and 43.2 PND (bw 221.1, 224.1, 224.3 and 243.4** g), respectively at 0, 10, 100 and 1000 mg/kg bw/d
- *haematological and clinical biochemistry findings if available :* no treatment related effect observed (no more information available)
- *effects on sperm :* not examined
- *female reproductive performance (data in females treated with propylparaben) :*
  - *mean number of implantations :* 14.3, 17.4**, 16.1 and 15.6, respectively at 0, 10, 100 and 1000 mg/kg bw/d
  - *oestrous cycle :* mean number of cycle : 3.2, 3.3, 3.2 and 3.0, respectively at 0, 10, 100 and 1000 mg/kg bw/d
    mean duration : 4.19, 4.43, 4.29 and 4.29 d, respectively at 0, 10, 100 and 1000 mg/kg bw/d
  - *mating index :* 93.3, 86.7, 93.3 and 93.3 %, respectively at 0, 10, 100 and 1000 mg/kg bw/d
  - *fertility index :* 86.7, 80.0, 93.3 and 93.3 %, respectively at 0, 10, 100 and 1000 mg/kg bw/d
  - *conception rate :* 92.9, 92.3, 100.0 and 100.0 %, respectively at 0, 10, 100 and 1000 mg/kg bw/d

  - *duration of gestation :* 21.8, 21.8, 22.2 and 21.9 d, respectively at 0, 10, 100 and 1000 mg/kg bw/d
  - *live birth index :* 88.96, 88.20, 89.72 and 92.36 %, respectively at 0, 10, 100 and 1000 mg/kg bw/d
- *male reproductive performance (male treated with propylparaben) :*
  - *mating index ((nb of males mating/nb of males placed for mating)*100) :* 100 % in all groups
  - *fertility index :* 92.9, 93.3, 80.0 and 86.7 %, respectively at 0, 10, 100 and 1000 mg/kg bw/d
- *reproductive performance for untreated females mated with treated males (GD 13 caesarean section) :*
  - *mean nb of corpora lutea :* 17.8, 17.9, 18.9 and 17.0, respectively at 0, 10, 100 and 1000 mg/kg bw/d
  - *mean nb of implantation sites :* 16.8, 17.0, 17.4 and 15.8, respectively at 0, 10, 100 and 1000 mg/kg bw/d
  - *mean nb of live embryos* : 15.8, 15.6, 16.5 and 15.3, respectively at 0, 10, 100 and 1000 mg/kg bw/d
  - *mean % of pre-implantation loss :* 5.74, 5.06, 7.76 and 7.88 %, respectively at 0, 10, 100 and 1000 mg/kg bw/d
  - *mean % of post-implantation loss :* 5.15, 8.15, 5.10 and 3.68 %, respectively at 0, 10, 100 and 1000 mg/kg bw/d
  - *mean nb of early resorptions + dead embryos :* 0.9, 1.4, 0.9 and 0.6, respectively at 0, 10, 100 and 1000 mg/kg bw/d
- *necropsy findings :* no treatment related effect observed
- *organ weight :* higher absolute and relative uterus weight at the highest dose group (+ 36% and + 43% compared to control, respectively) : absolute : 0.6357, 0.6051, 0.5451 and 0.8651 g, respectively at 0, 10, 100 and 1000 mg/kg bw/d and relative : 0.226, 0.227, 0.206 and 0.324* %, respectively at 0, 10, 100 and 1000 mg/kg bw/d

  no more information available
- *histopathological findings:* no treatment related effect observed (no more information available)

For pups/litters F2 (per dose):

- *live birth index :* 88.96, 88.20, 89.72 and 92.36 %, respectively at 0, 10, 100 and 1000 mg/kg bw/d
- *sex ratio :* 49.33, 48.22, 48.06 and 43.69 % of males: 88.96, 88.20, 89.72 and 92.36 %, respectively at 0, 10, 100 and 1000 mg/kg bw/d
- *viability index (pups surviving 4 days/total births) :* 100.0, 99.56, 98.59 and 99.04 %, respectively at 0, 10, 100 and 1000 mg/kg bw/d
- *clinical signs :* no effect observed (no more information available)

- *mean litter weight :* no effect observed (examined on PND 0 and 3) (no more information available)
- *external, soft tissue and skeletal malformations and other relevant alterations :* no malformed pups at any dose level (no more information available)

3.10.1.5 Gazin *et al.*, 2013

Study reference:

Gazin *et al.*, 2013, Oral propylparaben administration to juvenile male Wistar rats did not induce toxicity in reproductive organs, Toxicological Sciences

Detailed study summary and results:

Test type

Preliminary study to assess pharmacokinetic parameters such as time and concentration at peak plasma concentration, distribution volume, elimination t1/2 and renal clearance.

Main study : study design based on other studies already published and performed to assess the effects of parabens on the male reproductive system (with male rats treated with similar oral doses, from weaning to adulthood)

GLP

Test substance

- Propylparaben
- *Degree of purity :* 100%

Test animals

- *Species/strain/sex :* rat / Wistar / male
- *No. of animals per sex per dose :* Preliminary pharmacokinetic study : 18 males/dose (except for control group : 3 rats)

  Main study : 20 male/group (divided into 2 subgroups : the first one was sacrificed and necropsied at the end of the 8-week treatment period and the second after a 26-week washout period (to cover 3 spermatogenic cycles) + Satellite groups (juvenile toxicity study) : 17 male/ group for treated group and 9 male for control group (for TK study)
- *Age and weight at the study initiation :* 24d old and 85 to 120 g on dosing day (PND 31) for preliminary study

Administration/exposure

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

  Preliminary study : single exposure on PND 31 (all animals sacrificed after time point H24)

Main study : start at PND 21 and lasted for 8 weeks (necropsy : first subgroup was sacrificed and necropsied at the end of the 8-week treatment period and the second subgroup after a 26-week washout period)

- *doses/concentration levels :* 0, 3, 10, 100 and 1000 mg/kg bw/d
- *vehicle:* 1% hydroxyethylcellulose
- *actual doses (mg/kg bw/day) :* on the first day of administration (preliminary study), routine analysis demonstrated that the actual doses for the 10 and 100 mg/kg bw were outside of the specifications (with actual doses of 5.71 and 47 mg/kg bw, respectively). On PND 77, actual dose of the 10 mg/kg bw group was equivalent to 7.8 mg/kg bw and this level of exposure was taken into account when performing the pharmacokinetic study.

Results and discussion

Preliminary pharmacokinetic study (single exposure on PND 31) :

- *absorption :* rapidly absorbed (Tmax was reached between 5 and 30 min after ingestion)
- *distribution :* volume of distribution were 4.8 and 9.41 l/kg at 10 and 100 mg/kg bw
- *elimination :* rapid (with T1/2 of 47 and 58 min at 10 and 100 mg/kg bw, respectively)
- *clearance :* 4.20 and 6.68 (l/h)/kg at 10 and 100 mg/kg bw, respectively.

Satellite groups (juvenile toxicity study) :

- *Total propylparaben exposure :* statistically significantly reduced on PND77 (treatment day 56) in comparison with PND21 (treatment day 1).

No propylparaben detected in plasma from control group.

Free plasma propylparaben were low and quantifiable only at 100 and 1000 mg/kg bw until 8h after treatment with decreased exposure by PND77.

Table 56 : exposure to propylparaben at the start and the end of the treatment in Juvenile animals

Doses (mg/kg bw/d)	Time point (PND)	C_{max} (ng/ml)	T_{max} (min)	T (h)	AUC_{0-8h} (mg.h/ml)
3	Start (21)	786	15	1	408
	End (77-78)	500	15	4	538
1000	Start (21)	25003	30	8	148840
	End (77-78)	12030	15	4	47760

Main study :

- *time of death during the study and whether animals survived to termination :* no unscheduled death
- *clinical observations :* 1000 mg/kg bw/d : hypersalivation (through the end of the treatment period)

No other clinical sign reported

- *body weight data :* slightly increased at the highest dose (approx.. + 7% compared to control group)
- *sexual maturation :* mean day of balano-preputial separation : 44, 44, 44, 43 and 43 PND, respectively at 0, 3, 10, 100 and 1000 mg/kg bw/d

- *plasma hormone levels :*

Table 57 : plasma hormone levels (at the end of treatment)

Dose level (in mg/kg bw/d)	0	3	10	100	1000
Testosterone (nmol/l)	16.9	17.6	21.2	22.9	18.9
LH (ng/ml)	0.64	0.66	0.71	0.51	0.62
FSH (ng/ml)	13.6	12.7	12.4	13.4	12.5

- *sperm parameters :*
  - *mean epididymal sperm count :* 428, 501, 449, 473 and 547, respectively at 0, 3, 10, 100 and 1000 mg/kg bw/d
  - *epididymal sperm motility :*

Table 58 : Epididymal sperm motility

Dose level (in mg/kg bw/d)	0	3	10	100	1000
Motile sperm ratio (%)	81.1	88.2	71.4	85.5	85.8
VAP (µm/s)	162.5	162.2	143.8	152.1	153.6
VSL (µm/s)	111	111.4	97.2	102.5	103.1
VCL (µm/s)	348.2	332.5	305.3	322.3	316.2
ALH (µm)	14.5	14.5	13.4	14	14.3
STR (%)	67	68	60	67	66
LIN (%)	33	35	30	33	34

  - *mean sperm count in testis :* in the first subgroup (at the end of treatment period) : 153.9, 144.4, 145.2, 151.3 and 162.3 million sperm/g testis, respectively at 0, 3, 10, 100 and 1000 mg/kg bw/d

    in the second subgroup (at the end of recovery period) : 110.3, 103.1, 106.0, 111.2 and 105.4 million sperm/g testis, respectively at 0, 3, 10, 100 and 1000 mg/kg bw/d

- *organ weight :* no effect observed
  - *mean testis weight :* at the end of treatment period : 1.81, 1.78, 1.76, 1.74 and 1.77 g, respectively at 0, 3, 10, 100 and 1000 mg/kg bw/d

    at the end of recovery period : 1.93, 2.03, 1.96, 2.11 and 2.14 g, respectively at 0, 3, 10, 100 and 1000 mg/kg bw/d

- *histopathological findings:*
  - *at the end of treatment period :*

    in control group : no effect observed

    at 3 mg/kg bw/d : minimal focal or multifocal tubular atrophy/hypoplasia in testis of 3 males (out of 10)

at 10 mg/kg bw/d : one male had severe tubular atrophy/hypoplasia in testis + small epididymides + atrophy and aspermia in epididymides

at 100 mg/kg bw/d : no effect observed

at 1000 mg/kg bw/d : minimal focal or multifocal tubular atrophy/hypoplasia in 1 male (out of 10)

- *at the end of recovery period :*

in control group : minimal focal or multifocal tubular atrophy/hypoplasia in testis of 3 males (out of 10)

at 3 mg/kg bw/d : no effect observed

at 10 mg/kg bw/d : minimal focal or multifocal tubular atrophy/hypoplasia in testis of 1 males (out of 10)

at 100 mg/kg bw/d : no effect observed

at 1000 mg/kg bw/d : 1 male had small testes with severe diffuse hypospermatigenesis, decreased nb of germ cells, diffuse bilateral aspermia in epididymides

3.10.1.6 Oishi, 2002

Study reference:

Oishi S., 2002, Effects of propylparaben on the male reproductive system, Food and Chemical Toxicology, 40, 1807 – 1813.

Detailed study summary and results:

Test type

No OECD guideline followed

Wistar rats exposed to propylparaben to examine the effects on the male reproductive system (male reproductive organ weight, sperm count and serum testosterone concentration)

Test substance

- propylparaben
- *Degree of purity :* ≥ 99 %

Test animals

- *Species/strain/sex :* rats / Wistar / immature male
- *No. of animals per sex per dose :* 8 males/dose
- *Age and weight at the study initiation :* 19 to 21 days and 52.5 ± 2.17 g

Administration/exposure

- *route of administration :* oral, feed
- *duration and frequency of test/exposure period :* 4 weeks

- *doses/concentration levels, rationale for dose level selection :* 0, 0.01, 0.10 and 1.0 % (corresponding approx.. to 0, 12.4, 125 and 1290 mg/kg bw/d)
- *post exposure observation period :* no, animals were killed after 4 weeks of exposure
- *vehicle:* corn oil

Results and discussion

- *mortality and time to death (if occurring) :* no animals died
- *description, severity, time of onset and duration of clinical signs :* not mentioned
- *body weight :* no information available on the daily body weight examination
- *food consumption :* similar in all groups
- *ophthalmologic findings :* not examined
- *haematological findings :* not examined
- *clinical biochemistry findings:* not examined
- *sperm counts in the cauda epidydimis :*
    - reserves (number of sperms/cauda epididymis) : 43.6, 31.1, 25.7* and 22.5* $x10^7$/cauda, respectively at 0.0, 0.01, 0.1 and 1 %
    - concentration (number of sperms/ g of cauda epididymis) : 108, 70.8, 63.1* and 48.8* $x10^7$/g, respectively at 0, 0.01, 0.1 and 1 %
- *sperm production in the testis :*
    - DSP : 37.5, 26.2*, 27.0* and 25.9* $x10^6$, respectively at 0, 0.01, 0.1 and 1 %
    - efficiency : 30.0, 20.6*, 22.4* and 21.4* $x10^6$, respectively at 0, 0.01, 0.1 and 1 %
- *mean testosterone concentration in the serum :* 9.08, 8.20, 7.17 and 5.86* ng/ml, respectively at 0, 0.01, 0.10 and 1 %
- *gross pathology findings:* not mentioned
- *organ weight :* no treatment related effects observed

Table 59 : FBW and reproductive organ weight (in g or %)

Dose level (in %)		0	0.01	0.10	1.0
FBW		276	280	274	261*
Testes	Abs	2.65	2.67	2.60	2.60
	Rela	0.961	0.955	0.950	0.999
Epididymides	Abs	0.395	0.405	0.416	0.410
	Rela	0.143	0.145	0.152	0.157
Seminal vesicles	Abs	0.500	0.559	0.505	0.473
	Rela	0.181	0.200	0.184	0.182
Ventral prostates	Abs	0.266	0.310	0.288	0.261
	Rela	0.094	0.111	0.105	0.100

Preputial glands	Abs	0.196	0.207	0.171	0.185
	Rela	0.071	0.074	0.062	0.072

* : $p < 0.05$

- *histopathology findings:* not examined

3.10.1.7 Prenatal developmental toxicity study (Anonymous, 2019)

Study reference:

Anonymous, 2019

Detailed study summary and results:

Test type

OECD TG 414

GLP

Test substance

- propylparaben
- *Degree of purity :* 99.7 %

Test animals

- *Species/strain/sex :* rats / Wistar / pregnant females
- *No. of animals per sex per dose :* 25 pregnant females/dose
- *Age and weight at the study initiation :* 11-12 weeks (at the arrival to the lab), 197 to 264 g

Administration/exposure

- *Route of administration :* oral
- *duration and frequency of test/exposure period :* GD 5 to 19, daily (animals were killed and necropsied at GD 20).
- *doses/concentration levels, rationale for dose level selection :* 0, 100, 300 and 1000 mg/kg bw/d
- *vehicle:* 1 % hydroxyethyl-cellulose

Description of test design:

- *details on mating procedure (M/F ratios per cage, length of cohabitation, proof of pregnancy) :* after an acclimation period of at least 5 days, females were paired with males (1 male to 2 females per cage)

Results and discussion

For P (per dose):

- *time of death during the study and whether animals survived to termination :* no animals died during the study period

- *clinical observations:* moving bedding was observed in 16 females of the highest dose and increased salivation in 5 females of this dose. These signs were noted immediately after administration and observed during a short period.

  5, 4, 7 and 12 animals exhibited piloerection, respectively at 0, 100, 300 and 1000 mg/kg bw/d.

- *body weight data :*

Table 60 : body weight data (in g)

Dose level (in mg/kg bw/d)	0	100	300	1000
GD 0	235.20 (20)	232.87 (23)	231.52 (21)	231.79 (24)
GD 5	251.55 (20)	246.04 (23)	246.35 (20)	247.35 (23)
GD 11	268.85 (20)	264.74 (23)	262.35 (20)	263.35 (23)
GD 20	340.45 (20)	335.57 (23)	332.71 (21)	334.17 (24)

( ) : number of animals examined

- *food consumption :* no significant effect observed but slightly reduced at the mid and high dose groups (GD 0 – 20 : 384.26, 385.00, 370.86, 365.46 g, respectively at 0, 100, 300 and 1000 mg/kg bw/d)
- *mean number of implantations, corpora lutea :*
  - *corpora lutea :* 12.90, 12.70, 12.62, 13.21, respectively at 0, 100, 300 and 1000 mg/kg bw/d
  - *implantation sites :* 11.40, 11.96, 11.76 and 12.04, respectively at 0, 100, 300 and 1000 mg/kg bw/d
- *mean % of pre- and post-implantation loss :*
  - *pre- :* 12.57, 5.93, 6.95 and 8.71 %, respectively at 0, 100, 300 and 1000 mg/kg bw/d
  - *post- :* 6.23, 8.95, 5.36 and 8.07 %, respectively at 0, 100, 300 and 1000 mg/kg bw/d
- *mean resorptions :*
  - *early :* 0.75, 1.00, 0.62 and 1.00, respectively at 0, 100, 300 and 1000 mg/kg bw/d
  - *late :* 0.00, 0.04, 0.00 and 0.00, respectively at 0, 100, 300 and 1000 mg/kg bw/d
  - *total :* 0.75, 1.04, 0.62 and 1.00, respectively at 0, 100, 300 and 1000 mg/kg bw/d
- *number of live births :* 10.70, 10.91, 11.14 and 11.08, respectively at 0, 100, 300 and 1000 mg/kg bw/d
- *necropsy findings :* no effects observed
- *body weight change and gravid uterine weight, including optionally, body weight change corrected for gravid uterine weight :*

Table 61 : uterus and adjusted maternal weight (in g)

Dose level (in mg/kg bw/d)	0	100	300	1000
Terminal bw	340.45	335.57	332.71	334.17

Uterus weight	58.84	60.24	61.63	61.78
Adjusted maternal weight	281.61	275.32	271.08	272.39

- *histopathological findings:* no information available

For F1 pups/litters (per dose):

- *mean number of live pups (litter size) :* 10.70, 10.91, 11.14 and 11.08, respectively at 0, 100, 300 and 1000 mg/kg bw/d
    - *mean number of males :* 5.45, 5.96, 5.86 and 4.92, respectively at 0, 100, 300 and 1000 mg/kg bw/d
    - *mean number of females :* 5.25, 4.96, 5.29 and 6.17, respectively at 0, 100, 300 and 1000 mg/kg bw/d
- *mean number of dead foetuses :* no dead foetuses observed
- *sex ratio :* 1.34, 1.59, 1.46 and 0.87 males/females, respectively at 0, 100, 300 and 1000 mg/kg bw/d
- *mean litter or pup weight by sex and with sexes combined*
    - *mean foetus weight :* 3.64, 3.59, 3.69 and 3.67 g, respectively at 0, 100, 300 and 1000 mg/kg bw/d
    - *mean litter weight :* 38.24, 39.26, 40.94 and 40.56 g, respectively at 0, 100, 300 and 1000 mg/kg bw/d
    - *mean male litter weight :* 19.77, 21.97, 22.11 and 18.60 g, respectively at 0, 100, 300 and 1000 mg/kg bw/d
    - *mean female litter weight :* 18.47, 17.29, 18.83 and 21.96 g, respectively at 0, 100, 300 and 1000 mg/kg bw/d
- *external, soft tissue and skeletal malformations and other relevant alterations :*
    - *external examination :* no treatment related effect observed : tail haematoma (in 1 control), flank haematoma (in 1 low dose), head lateral haematoma (in 1 mid dose), ventral thoracic region haematoma (in 1 high dose), forelimb short (in 1 high dose)
    - *visceral examination :* no treatment related effect observed

Table 62 : Incidence of foetal visceral findings

Dose level (in mg/kg bw/d)	0	100	300	1000
Ureter (L) convoluted	7	15	11	12
Ureter (R) convoluted	0	1	0	1
Ureter (B) convoluted	2	4	1	3
Ureter (L) dilated	5	9	5	7
Ureter (R) dilated	6	4	2	6
Ureter (B) dilated	17	23	19	23
Umbilical artery transposed	13	14	15	18
Urinary bladder spotted red	1	3	4	2

Spleen discoloured white	0	0	0	1
Lung (R) discoloured red	0	1	0	0
Liver discoloured dark	3	2	0	3
Liver spotted white	0.99	0.00	0.00	0.00
Renal pelvis (R) dilated	1	1	1	1
Renal pelvis (L) dilated	0	1	0	0
Renal pelvis (B) dilated	0	1	0	1
Thymus cranial (R) long	1	1	3	0
Adrenal glands (B) spotted red	7	6	4	7
Adrenal glands (B) spotted dark	0	0	1	0
Kidney (R) discoloured red	0	1	0	0
Thymus spotted red	0	0	2	0

(B) : bilateral ; (R) : right ; (L) : left

- *craniofacial examination :* no treatment related effect observed

Table 63 : incidence of craniofacial findings

Dose level (in mg/kg bw/d)	0	100	300	1000
Ventricle (3rd) slightly dilated	0	0	1	0
Ventricle (3rd) dilated	0	1	1	2
Ventricle (lateral) (R) dilated	0	1	0	0
Ventricle (lateral) (B) dilated	0	1	1	0
Ventricle (lateral) (B) slightly dilated	8	10	8	14
Ventricle (lateral) (L) slightly dilated	2	4	6	4
Ventricle (lateral) (R) slightly dilated	0	0	1	3
Head subcutaneous haematoma	3	1	1	0
Head subcutaneous oedema	0	0	0	1
Subdural haematoma	1	0	1	0

(B) : bilateral ; (R) : right ; (L) : left

- *skeletal examination :* no treatment related effect observed

Table 64 : Incidence of skeletal findings

Dose level (in mg/kg bw/d)		0	100	300	1000
Skull	Skull auditory ossicles increased ossification	3	5	7	4
	Skull basioccipital incomplete ossification	3	3	6	1
	Skull basisphenoid incomplete ossification	3	3	1	0
	Skull bony labyrinth increased ossification	0	1	0	0
	Skull exoccipital incomplete ossification	0	1	0	0
	Skull frontal incomplete ossification	10	7	5	2

	Skull orbital socket region (L) increased ossification	15	16	18	13
	Skull orbital socket region (R) increased ossification	1	1	3	7
	Skull parietal (B) incomplete ossification	22	26	17	16
	Skull parietal (L) incomplete ossification	2	0	0	0
	Skull parietal (R) incomplete ossification	7	12	3	7
	Skull premaxxila (B) incomplete ossification	0	0	0	2
	Skull squamosal (B) incomplete ossification	6	10	5	6
	Skull squamosal (L) incomplete ossification	2	0	1	0
	Skull squamosal (R) incomplete ossification	1	2	1	1
	Skull supraoccipital incomplete ossification	53	60	41	45
	Skull zygomatic arch (B) incomplete ossification	7	7	5	2
	Skull zygomatic arch (L) incomplete ossification	0	0	0	2
	Skull zygomatic arch (R) incomplete ossification	1	3	1	2
Scapula	Markedly bent (B)	0	1	1	0
	Incomplete ossification (B)	0	0	0	1
	Slightly bent (B)	1	0	0	0
	Moderately bent (L)	1	1	0	0
	Slightly bent (L)	0	2	0	0
	Markedly bent (R)	4	2	0	0
	Moderately bent (R)	2	1	1	0
	Slightly bent (R)	2	2	0	1
Sternebra	Sternebra (1st) incomplete ossification	0	0	0	2
	Sternebra (2nd) incomplete ossification	7	0	2	2
	Sternebra (2nd) unossified	0	0	0	2
	Sternebra (3rd) incomplete ossification	0	0	0	2
	Sternebra (4th) incomplete ossification	0	0	0	1
	Sternebra (5th) incomplete ossification	32	28	17	31
	Sternebra (5th) unossified	2	0	0	3
	Sternebra (6th) incomplete ossification	90	84	84	79
	Sternebra (6th) unossified	1	0	0	3
Ribs	Fused	0	0	0	2
	Branched	0	0	0	1
	Absent	0	0	0	2
	Incomplete ossification	0	0	0	1
	Wavy	43	44	38	37
Vertebra	Caudal arch incomplete ossification	1	0	0	0
	Caudal fused	10	12	8	15
	Cervical arch(es) incomplete ossification	4	1	2	2
	Cervical arch(es) slightly irregular ossified	3	1	2	3

	Cervical arch(es) moderately irregular ossified	1	3	5	6
	Cervical arch(es) misshapen	0	0	0	1
	Cervical centrum(-tra) unossified	87	96	89	86
	Lumbar arch(es) increased ossification	4	7	2	3
	Lumbar centrum(-tra) hemicentric ossification	0	0	0	1
	Lumbar arch(es) unossified	0	0	0	1
	Lumbar centrum(-tra) split	0	0	0	1
	Lumbar centrum(-tra) asymmetric ossification	0	1	0	0
	Sacral arch(es) incomplete ossification	1	0	0	0
	Sacral centrum(-tra) incomplete ossification	0	0	0	1
	Sacral centrum(-tra) slightly irregular ossification	0	0	0	1
	Thoracic arch(es) malpositioned	0	0	0	1
	Thoracic arch(es) incomplete ossification	1	0	0	0
	Thoracic arch(es) small	0	0	0	1
	Thoracic arch(es) unossified	0	0	0	1
	Thoracic centrum(-tra) slightly irregular ossified	17	12	12	15
	Thoracic centrum(-tra) moderately irregular ossified	3	2	4	4
	Thoracic centrum(-tra) unossified	0	0	0	1
	Thoracic centrum(-tra) malpositioned	0	0	0	1
Forelimb	Humerus markedly misshapen	0	0	0	1
	Humerus moderately misshapen	4	4	1	0
	Metacarpal(s) unossified	11	9	3	12
	Phalanges unossified	112	119	114	118
Hindlimb	Metatarsal(s) unossified	0	0	0	1
	Femur incomplete ossification	0	0	0	2
	Fibula incomplete ossification	0	0	0	2
	Tibia incomplete ossification	0	0	0	2
Pelvic griddle	Caudal shift (B)	6	1	5	4
	Caudal shift (L)	1	4	3	3
	Caudal shift (R)	1	0	2	0
	Ilium incomplete ossification	0	0	0	2
	Pubis incomplete ossification	5	0	0	2
	Ischium incomplete ossification	0	0	0	2
Clavicula	Slightly misshapen (R)	1	0	0	0

(B) : bilateral ; (R) : right ; (L) : left

3.10.1.8 Shaw and deCatanzaro, 2009

Study reference:

Shaw J and deCatanzaro D., 2009, Estrogenicity of parabens revisited: Impact of parabens on early pregnancy and an uterotrophic assay in mice, Reproductive toxicology, 28, 26-31

Detailed study summary and results:

Test type

Two different studies were explained in the article : one with butylparaben (Exp. 1) and the second one with propylparaben (Exp. 2). As these 2 studies did not induce the expected findings, therefore an uterotrophic assay was additionally performed with butylparaben (Exp. 3)

Test substance

- Propylparaben for Exp. 2 and butylparaben for Exp. 1 and 3
- *Degree of purity :* not mentioned

Test animals

- *Species/strain/sex :* mice / CF-1 and CD-1/ both sexes
- *No. of animals per sex per dose :* not mentioned
- *Age and weight at the study initiation :* average BW was 36.9 +- 0.26 and 35.0 +- 0.45 g for CF-1 and CD-1 mice (no sex distinction), respectively. All females were between 100 and 180 days old and males were between 150-420 days old.

Experiment 1 :

Administration/exposure

- *Route of administration :* subcutaneous injection
- *duration and frequency of test/exposure period :* once a day, for 4 days
- *doses/concentration levels, rationale for dose level selection :* 0, 0.05, 0.5, 5, 10, 15, 20, 30 and 35 mg butylparaben; other females were exposed to 17β-estradiol
  butylparaben and estradiol were dissolved in peanut oil: 0.05 and 0.5 mg butylparaben in 0.05 ml peanut oil; estradiol in 0.05 ml peanut oil; 5 mg butylparaben in 0.1 ml peanut oil; 10, 15, and 20 mg butylparaben in 0.3 ml peanut oil; 30 and 35 mg butylparaben in 0.45 ml peanut oil.
- *vehicle:* peanut oil

Description of test design:

CF-1 females were firstly weighed then separated (1 per cage) at the start of the experiment

After 4 days, each female mice was paired with a previously proven fertile male in a new cage

Females were then observed 3 times a day for sperm plug. When the sperm plug was seen, it was considered as day 0 of gestation (GD1). Males were removed from the cage before the first injection.

Subcutaneous injection of butylparaben (purity unspecified) was administered daily from GD1 to GD4, starting 3 to 6 hours into the dark cycle. Each injection was given at four different sites to reduce the risk of local irritation (right and left flanks, rear middle area and scruff of the neck)

Females were placed in a new cage 14 to 16 days after mating than left without any disturbance until delivery.

After parturition, the number of pups born was reported, pups BW was recorded on PND3 and remaining pups' survival rate was measured on PND5. Due to an experimental error, no data was monitored in the groups exposed to 5 and 10 mg after PND3.

An additional group was exposed to the highest dose in order to confirm the obtained results with a distinct source of butylparaben. Females received 35 mg butylparaben (purity > 99 %) in 0.45 ml peanut oil. A control group received the same volume of peanut oil at the same relevant site of injection depending of the day of treatment.

Experiment 2 :

Administration/exposure

- *Route of administration :* subcutaneous injection
- *duration and frequency of test/exposure period :* daily on GD 1 to GD 4
- *doses/concentration levels, rationale for dose level selection :* 35 or 40 mg of propylparaben
- *vehicle:* propylparaben was dissolved in DMSO (0.05 ml)

Description of test design:

Goal was to see if high doses of propylparaben would impact gestation and if the substance used direct measures of uterine implantation sites

CF-1 females were inseminated as in experiment 1.

Females received either 0.05 ml DMSO or 35 mg propylparaben in 0.05 ml DMSO or 40 mg propylparaben in 0.05 ml DMSO

Treatment occurred from GD1 to GD4. On GD6, the mice were euthanized via CO2 asphyxiation and each uterus was removed after abdominal incision. The number of visible implantation sites in the uterus was counted as described by Berger et al. (2008) "Impact of acute bisphenol A exposure upon intrauterine implantation of fertilized ova and urinary 17-βestradiol and progesterone levels" in Reproductive toxicology 26:94-9.

The used definition of an implantation site was "a small, round swelling in an otherwise smooth, uninterrupted uterine horn".

Experiment 3 :

Administration/exposure

- *Route of administration :* subcutaneous injection
- *duration and frequency of test/exposure period :* daily injection, once a day, for 3 consecutive days
- *doses/concentration levels, rationale for dose level selection :* butylparaben: doses of either 0.735, 7.35 or 35 mg; selection rationale specified: included doses able to elicit an uterotrophic response according to Lemini et al. (2003) in "In vivo and in vitro estrogen bioactivities of alkyl parabens" in Toxicol Ind Health 19:69-79, and to include the highest dose of the Experiment 1.

- *control group:* positive control group received 500 ng 17-βestradiol
- *vehicle:* peanut oil; 0.45 ml per injection

Description of test design:

Adult CD-1 and CF-1 female mice were used. First they were bilaterally ovariectomized under sodium pentobarbital anaesthesia. Animals were caged per groups of 5 for a 24-h recovery period and then were isolated.

A randomization was performed to assign each animal to a treatment group (butylaraben – treatment group- or vehicle only – negative control group; or estradiol – positive control group).

Administration of treatment was made via subcutaneous injection, once a day, on three consecutive days starting from day 27 post ovariectomy. A positive control group received subcutaneous injections of 17-βestradiol. Exposed mice receive either 0.735, 7.35 or 35 mg butylparaben or 500 ng 17βestradiol. The control group received only peanut oil. Injection sites were changed every day to avoid any local irritation (right and left flank and scruff of the neck and administration occurred 3-6 h into the dark cycle. Butylparaben and 17βestradiol were dissolved in 0.45 ml peanut oil.

Age and weight were counterbalanced across conditions. 24h after the last injection (Day 30 post ovariectomy), mice were weighed again and euthanized with Co2. Hysterectomies were performed on each mouse via abdominal incision. The sutures made to avoid excessive bleeding after ovariectomy were removed by just excising the uterus at the base of the said sutures. Fat and mesentery were removed from the uteri, then the organ was put in pre-weighed micro-tubes to get the wet mass of each uterus. Uterine dry weight was obtained after 21 days of tissue storage in calcium sulphate crystals.

Results and discussion

Exp. 1 :

- *skin irritation :* reported on most animals exposed to more than 0.5 mg butylparaben (one or more injection sites, especially on the scruff of the neck). Severity and size were proportional to the dose. 2 animals were taken out of the study (one exposed to 20 and one to 35 mg butylparaben) due to poor health and lesions in the first days following injections. No differences seen between control animals (different volumes of peanut oil) in any measurement. Thus their data were put together for subsequent statistical analyses.
- *Average number of pups :* no impact of butylparaben at any dose on the number of born pups, while administration of 17βestradiol induced all pregnancies termination. (see Figure 3)

Figure 3 : mean nb of pups born (Shaw J and deCatanzaro D., 2009)

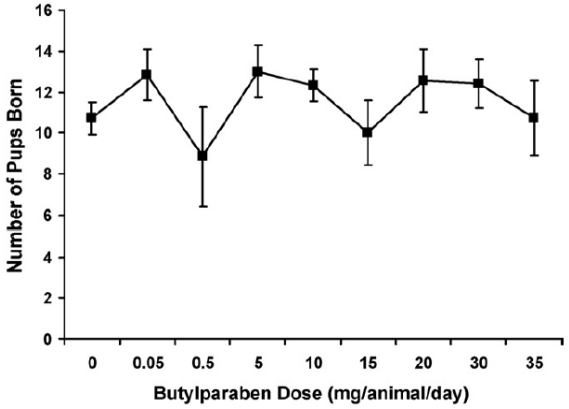


Fig. 1. The mean (±S.E.) number of pups born following subcutaneous administration of butylparaben on days 1–4 of gestation in Experiment 1. 17β-Estradiol was administered to an additional group and terminated all pregnancies.

- *Other reproductive data :*

Table 65 : reproductive data

Dose level	Butylparaben (mg)									17βestradiol
	0	0.05	0.5	5	10	15	20	30	35	500 ng
Nb examined	38	6	7	5	6	15	14	15	15	8
% pregnant dams	86.8	100	71.4	100	100	80	85.7	93.3	73.3	0
Gestation duration (d)	19.5 ± 0.1	19.5 ± 0.2	19.4 ± 0.4	19.4 ± 0.2	19.7 ± 0.2	19.7 ± 0.2	19.5 ± 0.2	19.4 ± 0.2	19.6 ± 0.2	NA
Litter weight PND3 (g)	25.2 ± 2.7	31.5 ± 1.2	24.9 ± 6.6	N/A	N/A	25.6 ± 4.6	30.6 ± 4.3	30.1 ± 3.4	24.7 ± 4.7	NA
# alive pups on PND	9.4 ± 0.9	12.2 ± 1.1	8.9 ± 2.9	12.6 ± 1.3	10.7 ± 1.7	9.2 ± 1.7	11.4 ± 1.5	11.3 ± 1.4	9.5 ± 1.8	NA
% dying pups	12.5	5.2	0.0	3.1	13.5	8.0	9.1	8.6	13.0	NA

±S.E.; # = number; NA= not applicable

- *Nb of pregnant females :* In females exposed to 35 mg butylparaben from the second source, 7 out of 8 dams became pregnant and an average number of 11.8 ± 2.0 pups were born. In the control group, 5 out of 6 dams were pregnant and delivered 10.3 ± 0.9 pups, in average. The difference in the number of pups between both groups was not statistically significant (t test).

Exp. 2 :

- *Skin irritation :* noted in most animals exposed to 35 of 40 mg propylparaben, mostly on the scruff of the neck (but also on other sites)

- *Average number of implantation sites on GD6 :* no effect of propylparaben in the mean number of implantation sites. (see Figure 4)

Figure 4 : mean nb of intrauterine implantation sites (Shaw J and deCatanzaro D., 2009)

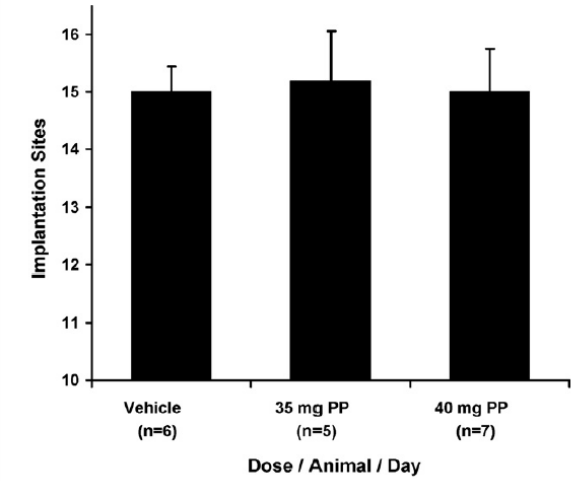


Fig. 2. The mean (±S.E.) number of intrauterine implantation sites for females receiving subcutaneous injections of propylparaben (PP) or DMSO vehicle on days 1–4 of gestation in Experiment 2.

Exp. 3 :

- *Absolute and relative wet and dry mean uteri weights :* results were similar for both strains. Butylparaben did not induce an increase in uteri weights, on the contrary to 17βestradiol which significantly increased uteri wet and dry absolute and relative weights.

Table 66 : uterus weight

Dose levels	Butylparaben (mg)				17βestradiol (ng)
	0	0.735	7.35	35	500
Strain CF-1					
n	7	8	8	8	7
Wet weight (mg)	29.2 ± 1.9	31.4 ± 1.6	31.4 ± 2.0	35.7 ± 2.2	16.8 ± 13.3*
Wet weight / 100g	81.4 ± 3.9	86.9 ± 3.5	86.1 ± 3.9	100.2 ± 5.4	320.4 ± 30.5*
Dry weight (mg)	8.57 ± 0.92	7.96 ± 0.38	7.98 ± 0.43	8.94 ± 0.57	20.6 ± 1.80*
Dry weight / 100g	23.8 ± 2.2	22.2 ± 1.4	22.0 ± 0.9	25.1 ± 1.5	56.6 ± 3.8*
Strain CD-1					
n	8	8	7	8	7
Wet weight (mg)	29.5 ± 4.4	50.2 ± 23.0	26.1 ± 1.2	33.4 ± 2.9	20.0 ± 5.0*
Wet weight / 100g	86.0 ± 12.6	145.2 ± 67.8	75.5 ± 4.5	96.0 ± 8.4	335 ± 12.5*
Dry weight (mg)	7.01 ± 0.85	11.54 ± 4.01	6.61 ± 0.41	7.98 ± 0.53	21.3 ± 1.18*
Dry weight / 100g	20.4 ± 2.4	33.4 ± 11.8	19.2 ± 1.6	22.9 ± 1.6	1.6 ± 3.3*

:P < 0.05

3.10.2 Human data

No available data

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

No available data

3.11 Specific target organ toxicity – single exposure

Hazard class not assessed in this dossier

3.12 Specific target organ toxicity – repeated exposure

Hazard class not assessed in this CLH dossier

3.13 Aspiration hazard

Hazard class not assessed in this CLH dossier

4 ENVIRONMENTAL HAZARDS

Hazard class not assessed in this CLH dossier

5 REFERENCES

Registration dossier : https://echa.europa.eu/registration-dossier/-/registered-dossier/13890

Full study report

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Sivaraman L., Pouliot L., Wang B., Brodie T., Graziano M. and McNerney M.E. (2018) : Safety assessment of propylparaben in juvenils rats. Ragulatory Toxicology and Pharmacology, 92, 370-381.

6 ABBREVIATIONS

* : p< 0.05

** : p< 0.01

*** : p<0.001

A/G : albumin/globulin ratio

Abs : absolute

AGD : ano-genital distance

Alat : alanine aminotransferase

Alb : albumin

ALH : amplitude of lateral head displacement

ALP : alkaline phosphatase

Approx. : approximately

Asat : aspartate aminotransferase

Baso : basophil

Bile ac. : bile acids

Bili-t : total bilirubin

Bw : body weight

Ca : calcium

Chol : cholesterol

Cl : chloride

Conc. : concentration

Creat : creatinine

DMSO : dimethym sulfoxide

DPP : day post-partum

DSP : daily sperm production

EOGRTS : Extended one-generation reproductive toxicity study

Eos : eosinophil

Exp : experiment

F : female

FBW : final body weight

FM : fast movements

FOB : functional observation battery

FR : fast rearings

GD : gestational day

GGT : gamma glutamyltransferase

Glob : globulin

GLP : good laboratory practice

HDW : haemoglobin conc. distribution width

Hg : haemoglobin

Ht : haematocrit

K : potassium

L. : left

LIN : linearity (VSL/VCL *100)

Lymph : lymphocyte

M : male

Max : maximum

MCH : mean corpuscular haemoglobin

MCHC : mean corpuscular haemoglobin concentration

MCV : mean corpuscular volume

Min : minimum

Mono : monocyte

Na : sodium

NA : not applicable

Nb : number

Neut : neutrophile

NT : not tested

P : phosphohrus

PC : positive control

Plt : platelet

PMD : post mating day

PND : post natal day

PP : post-partum

Prot : protein

PT : prothrombine time

PTT : partial thromboplastin time

R. : right

RBC : red blood cell

RDW : red cell volume distribution width

Rela : relative

SD : Sprague Dawley

SM : slow movemements

SR : slow rearings

St. De. : standard deviation

Stat : statistical

STR : straightness (VSL/VAP *100)

T3 : triiodothyronine

T4 : L-thyroxine

TG : test guideline

Tot : total

Trig : triglyceride

TSH : thyroid-stimulating hormone

VAP : average path velocity

VCL : curvilinear velocity

VSL : straight line velocity

WBC : white blood cell