CLH report

Proposal for Harmonised Classification and Labelling

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

Chemical name:

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

EC Number: 424-640-9

CAS Number: 202842-98-6

Index Number: /

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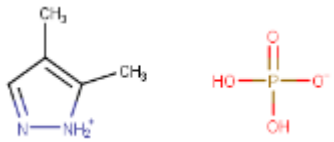
CONTENTS

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	3,4-dimethyl-1*H*-pyrazol-1-ium dihydrogen phosphate
Other names (usual name, trade name, abbreviation)	3,4-dimethyl-1H-pyrazol-1-ium dihydrogen phosphate 3,4-Dimethyl-1H-pyrazole phosphate DMPP 3,4-Dimethyl-1H-pyrazolium dihydrogenphosphate 3,4-Dimethyl-1H-pyrazoliumdihydrogenphosphat
ISO common name (if available and appropriate)	/
EC number (if available and appropriate)	424-640-9
EC name (if available and appropriate)	/
CAS number (if available)	202842-98-6
Other identity code (if available)	/
Molecular formula	C5H11N2PO4
Structural formula	
SMILES notation (if available)	/
Molecular weight or molecular weight range	194.13 g/mol
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	/
Description of the manufacturing process and identity of the source (for UVCB substances only)	/
Degree of purity (%) (if relevant for the entry in Annex VI)	/

1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum in multi-constituent substances)**	**Current CLH in Annex VI Table 3 (CLP)**	**Current self-classification and labelling (CLP)**
3,4-dimethyl-1H-pyrazol-1-ium dihydrogen	**≥ 95 - ≤ 100 %**	/	**Acute Tox. 4, H302 Eye Irrit. 2, H319**

Constituent (Name and numerical identifier)	Concentration range (% w/w minimum and maximum in multi-constituent substances)	Current CLH in Annex VI Table 3 (CLP)	Current self-classification and labelling (CLP)
phosphate			Repr. 2, H361fd STOT RE 2, H373

Table 3: Impurities (non-confidential information) if relevant for the classification of the substance

Impurity (Name and numerical identifier)	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3 (CLP)	Current self-classification and labelling (CLP)	The impurity contributes to the classification and labelling
No info available				

Table 4: Additives (non-confidential information) if relevant for the classification of the substance

Additive (Name and numerical identifier)	Function	Concentration range (% w/w minimum and maximum)	Current CLH in Annex VI Table 3 (CLP)	Current self-classification and labelling (CLP)	The additive contributes to the classification and labelling
No info available					

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 5: For substance with no current entry in Annex VI of CLP

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATEs	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	No current Annex VI entry										
Dossier submitter's proposal	TBD	3,4-dimethyl-1*H*-pyrazol-1-ium dihydrogen phosphate	424-640-9	202842-98-6	Repr. 1B Acute Tox. 4 STOT RE 2	H360FD H302 H373 (nasal cavity)	Dgr	H360FD H302 H373 (nasal cavity)		oral: ATE = 500 mg/kg bw	

Table 6: Reason for not proposing harmonised classification and status under public consultation

Hazard class	Reason for no classification	Within the scope of public consultation
Explosives	Hazard class not assessed in this dossier	No
Flammable gases (including chemically unstable gases)	Hazard class not assessed in this dossier	No
Oxidising gases	Hazard class not assessed in this dossier	No
Gases under pressure	Hazard class not assessed in this dossier	No
Flammable liquids	Hazard class not assessed in this dossier	No
Flammable solids	Hazard class not assessed in this dossier	No
Self-reactive substances	Hazard class not assessed in this dossier	No
Pyrophoric liquids	Hazard class not assessed in this dossier	No
Pyrophoric solids	Hazard class not assessed in this dossier	No
Self-heating substances	Hazard class not assessed in this dossier	No
Substances which in contact with water emit flammable gases	Hazard class not assessed in this dossier	No
Oxidising liquids	Hazard class not assessed in this dossier	No
Oxidising solids	Hazard class not assessed in this dossier	No
Organic peroxides	Hazard class not assessed in this dossier	No
Corrosive to metals	Hazard class not assessed in this dossier	No
Acute toxicity via oral route	**Acute Tox. Cat. 4 H302** **ATE (oral): 500 mg/kg bw**	Yes
Acute toxicity via dermal route	Data conclusive but not sufficient for classification	Yes
Acute toxicity via inhalation route	Data conclusive but not sufficient for classification	Yes
Skin corrosion/irritation	Hazard class not assessed in this dossier	No
Serious eye damage/eye irritation	Hazard class not assessed in this dossier	No
Respiratory sensitisation	Hazard class not assessed in this dossier	No
Skin sensitisation	Hazard class not assessed in this dossier	No
Germ cell mutagenicity	Hazard class not assessed in this dossier	No
Carcinogenicity	Hazard class not assessed in this dossier	No
Reproductive toxicity	**Repr. 1B H360FD**	Yes
Specific target organ toxicity-single exposure	Hazard class not assessed in this dossier	No
Specific target organ toxicity-repeated exposure	**STOT RE 2 H373 (nasal cavity)**	Yes
Aspiration hazard	Hazard class not assessed in this dossier	No
Hazardous to the aquatic environment	Hazard class not assessed in this dossier	No
Hazardous to the ozone layer	Hazard class not assessed in this dossier	No

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

3,4-dimethyl-1*H*-pyrazol-1-ium dihydrogen phosphate is a mono-constituent substance which is registered under REACH (1907/2006/EC) by means of a REACH full registration and a NONS registration.

The substance is currently not registered in annex VI of CLP.

The substance is self-classified in the full registration dossier as:

Acute Tox. 4, H302

Eye Irrit. 2, H319

Repr. 2, H361fd

STOT RE 2, H373

Notified self-classifications in the C&L inventory are the same as in the full registration dossier (22/11/2022 - 1 aggregated notification, 5 notifiers)

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

[A.] There is no requirement for justification that action is needed at Community level.

The substance is self-classified as Repr. 2, H361fd

Further detail on need of action at Community level
Acute toxicity and STOT RE : addition of ATE and specific target organ to the self-classification

5 IDENTIFIED USES

3,4-dimethyl-1*H*-pyrazol-1-ium dihydrogen phosphate is used by consumers, by professional workers (widespread uses), in formulation or re-packing, at industrial sites and in manufacturing. The substance is used in fertilisers.

6 DATA SOURCES

Registration dossier and C&L inventory: https://echa.europa.eu/substance-information/-/substanceinfo/100.102.315

Full study reports

7 PHYSICOCHEMICAL PROPERTIES

Table 7: Summary of physicochemical properties

Property	**Value**	**Reference**	**Comment (e.g. measured or estimated)**
Physical state at 20 °C and 101.3 kPa	solid	Anonymous, 1996	/
Melting/freezing point	164.5 °C (at 1013.25 hPa)	Anonymous, 1997	OECD TG 102

Property	Value	Reference	Comment (e.g. measured or estimated)
Boiling point	/	Anonymous, 1997	Not determinable because of methodological limitations
Relative density	1.511 (at 20 °C)	Anonymous, 1997	OECD TG 109 Air comparison pycnometer (for solids)
Vapour pressure	< 0 hPa (at 20 °C) < 0 hPa (at 50 °C)	Anonymous, 1997	EU A.4 (effusion method: by loss of weight or by trapping vaporisate)
Surface tension	70.7 mN/m (at 20 °C, conc.: 1 g/L)	Anonymous, 1997	OECD TG 115 EU A.5
Water solubility	Key: 132 g/L (at 25 °C, pH= 3) Supporting: 45.6 g/L (at 20 °C, pH= 7)	Anonymous, 1997 Anonymous, 1997	EU A.6 (flask method)
Partition coefficient n-octanol/water	Log Kow= 1.26 (at 25 °C, pH= 7)	Anonymous, 1997	EU A.8
Flash point	/	/	No data
Flammability	Preliminary screening test Effect observed No effect observed	Anonymous, 1996 Anonymous, 2017 Anonymous, 2017	EU A.10 UN Manual of tests and Criteria: Test N.4 UN Manual of tests and Criteria: Test N.4
Explosive properties	/	/	No data
Self-ignition temperature	No self-ignition up to the melting point	Anonymous, 1996	EU A.16
Oxidising properties	/	/	No specified study adequacy
Granulometry	D 10: mean 24.4 µM +/- 0.58 D 50: mean 96.4 µm +/- 2.92 D 90: mean 275.5 µm +/- 20.66	Anonymous, 2018	OECD TG 110 EPA OPPTS 830.7520 ISO 13320
Stability in organic solvents and identity of relevant degradation products	/	/	No data
Dissociation constant	Pka= 4.05 (at 22 °C)	Anonymous, 1998	OECD TG 112
Viscosity	/	/	No data

8 EVALUATION OF PHYSICAL HAZARDS

Hazard class not assessed in this dossier.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Not assessed in this dossier.

10 EVALUATION OF HEALTH HAZARDS

10.1 Acute toxicity - oral route

Table 8: Summary table of animal studies on acute oral toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels, duration of exposure	Value LD_{50}	Reference
Acute oral toxicity study By gavage GLP	Wistar rat 3 animals/Exp (3 M for the first and second Exp and 3 F for the third Exp)	3,4-dimethyl-1*H*-pyrazol-1-ium dihydrogen phosphate Purity: 97.1 %	2000 mg/kg bw for the first Exp 200 mg/kg bw for the second and third Exp Single exposure	200 – 2000 mg/kg bw	Anonymous, 1997

No human data or other data available.

10.1.1 Short summary and overall relevance of the provided information on acute oral toxicity

In an acute oral toxicity study (Anonymous, 1997), Wistar rats were given by gavage the test substance. The first experiment exposed once 3 males at a concentration of 2000 mg/kg bw. Three hours after exposure, one animal died and a second died after one day. Immediately after exposure, all animals exhibited impaired or poor general state, dyspnoea, apathy, abdominal position and staggering. One hour after, atonia was observed in all animals, while narcotic-like state was noted in 2 animals. The necropsy of the 2 males which died showed moderate dilatation of the urinary bladder, furthermore, one animal had erosion/ulcer and slight hyperaemia in glandular stomach. At the end of the post-exposure period, the male which survived did not have macroscopic findings at necropsy.

In the second experiment, 3 males were exposed once to 200 mg/kg bw of the test substance. During the post-exposure period of 14 days, no mortality was observed. Furthermore, animals did not exhibit clinical signs. At the end of the post-exposure period, necropsy did not reveal any findings.

A third experiment was performed and exposed 3 females once to the test substance at a concentration of 200 mg/kg bw. No mortality was observed during the post-exposure period, however, all animals also exhibited clinical signs only 1 hour after exposure, such as, impaired general state, dyspnoea, staggering and piloerection. Clinical signs were observed until day 3 after exposure. At the end of the post-exposure period, necropsy did not reveal any findings.

Based on the available results, the LD50 was comprised between 200 and 2000 mg/kg bw.

10.1.2 Comparison with the CLP criteria

Table 9: Comparison with the CLP criteria regarding acute toxicity via oral route

CLP criteria	Results of available studies
Acute toxicity category 4: oral LD50: > 300 but ≤ 2000 mg/kg bw	LD50 of the available study (Anonymous, 1997) was comprised between 200 and 2000 mg/kg bw.
Regarding ATE: based on the table 3.1.2 in the CLP	As only a range of LD50 was available and based on

Regulation ("conversion from experimentally obtained acute toxicity range values to acute toxicity point estimates") For a substance in category 4 oral route: the converted acute toxicity point estimate = 500 mg/kg bw	the table 3.1.2 of the CLP Regulation (Regulation (EC) No 1272/2008), an ATE of 500 mg/kg bw is warranted

10.1.3 Conclusion on classification and labelling for acute oral toxicity

Based on the available results, a classification as **Acute Tox. Cat. 4, H302 (Harmful if swallowed)** is warranted. Based on CLP regulation, an **$ATE_{(oral)}$ of 500 mg/kg bw** is warranted.

10.2 Acute toxicity - dermal route

Table 10: Summary table of animal studies on acute dermal toxicity

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance,	Dose levels duration of exposure	Value LD_{50}	Reference
Acute dermal toxicity study Semi-occlusive OECD TG 402 GLP	Wistar rat 5/sex/dose	3,4-dimethyl-1*H*-pyrazol-1-ium dihydrogen phosphate Purity: 99.4 %	2000 and 5000 mg/kg bw Single exposure of 24 hours	> 5000 mg/kg bw	Anonymous, 2017

No human data or other data available.

10.2.1 Short summary and overall relevance of the provided information on acute dermal toxicity

In an acute dermal toxicity study (Anonymous, 2017), groups of 5 male and 5 female Wistar rats were dermally exposed to the test substance at a concentration of either 2000 or 5000 mg/kg bw. The clipped application site was covered by semi-occlusive dressing during an exposure period of 24 hours. After removal of the semi-occlusive dressing, application site was rinsed with warm water and animals were observed during 14 days.

During observation period, no mortality was observed in any treated groups. Furthermore, no local or systemic effects were observed.

At the end of the observation period, animals were euthanized and necropsied. No macroscopic findings were noted in any animals.

Based on the available results, the LD50 was higher than 5000 mg/kg bw.

10.2.2 Comparison with the CLP criteria

Table 11: Comparison with the CLP criteria regarding acute toxicity via dermal route

CLP criteria	Results of available studies
Acute toxicity category 4: dermal LD50: > 1000 but ≤ 2000 mg/kg bw	No mortality occurred in the available study (Anonymous, 2017) LD50 > 5000 mg/kg bw

10.2.3 Conclusion on classification and labelling for acute dermal toxicity

Based on the available results, a classification as Acute toxicity via dermal route is not warranted.

10.3 Acute toxicity - inhalation route

Table 12: Summary table of animal studies on acute inhalation toxicity

Method, guideline, deviations if any	**Species, strain, sex, no/group**	**Test substance, , form and particle size (MMAD)**	**Dose levels, duration of exposure**	**Value** LC_{50}	**Reference**
Acute inhalation toxicity study Head-nose inhalation system Dust OECD TG 403 GLP	Rat (Wistar) 5/sex/group	3,4-dimethyl-1*H*-pyrazol-1-ium dihydrogen phosphate Purity: 97.1 % MMAD: 12.2 µm	5.5 mg/L Single exposure of 4 hours	> 5.5 mg/l	Anonymous, 1997

No human data or other data available.

10.3.1 Short summary and overall relevance of the provided information on acute inhalation toxicity

In an acute inhalation toxicity study (Anonymous, 1997), similar to OECD TG 403, 5 male and 5 female Wistar rats were exposed during 4 hours by a head-nose system to the test substance at a concentration of 5.5 mg/L.

During observation period of 14 days, no mortality was observed. However, all animals exhibited irregular and accelerated respiration, crust formation in nose and piloerection. After 3 days, all animals recovered.

Based on the available result, the LC50 was higher than 5.5 mg/L.

10.3.2 Comparison with the CLP criteria

Table 13: Comparison with the CLP criteria regarding acute toxicity via inhalation route

CLP criteria	Results of available studies
Acute toxicity category 4: inhalation (dusts and mists) LC50: > 1.0 but ≤ 5.0 mg/L	LC50 of the available study (Anonymous, 1997) was higher than 5.5 mg/L

10.3.3 Conclusion on classification and labelling for acute inhalation toxicity

Based on the available results, a classification as Acute toxicity via inhalation route is not warranted.

10.4 Skin corrosion/irritation

Hazard class not assessed in this dossier.

10.5 Serious eye damage/eye irritation

Hazard class not assessed in this dossier.

10.6 Respiratory sensitisation

Hazard class not assessed in this dossier.

10.7 Skin sensitisation

Hazard class not assessed in this dossier.

10.8 Germ cell mutagenicity

Hazard class not assessed in this dossier.

10.9 Carcinogenicity

Hazard class not assessed in this dossier.

10.10 Reproductive toxicity

10.10.1 Adverse effects on sexual function and fertility

Table 14: Summary table of animal studies on adverse effects on sexual function and fertility

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Two-generation reproductive toxicity study Rat (Wistar) 25/sex/group OECD TG 416 GLP	DMPP Purity: 97 % Conc.: 0, 20, 100 and 500/300 mg/kg bw/d Duration of exposure: F0 generation (F0M and F0F): 75 D before mating for M and F and until LD 21 for F. F1A pups (examined until PND 4 or 21) Second F0 generation (with same animals) (F0X and F0Y): 10 w premating and until	F0M and F0F parents (doses: 0, 20, 100 and 500 mg/kg bw/d): Mortality: mid dose: 1 M found dead (necropsy: malignant oligodendrioma) + 1 F sacrificed (necropsy: malignant lymphoma) Food cons.: lower at 500 mg/kg bw/d (approx. – 7 % in M and F premating period, - 13 % in F during gestation and – 26 % in F during lactation) Bw: sign lower in M and F at the highest dose Male fertility: 3 M of the highest dose did not mate and in total 8 M failed to have F pregnant Sperm parameters: NE Female fertility: mean days from estrous to estrous sign. increased at the highest dose (4.8 D vs 4.0 D in control) Female fertility index: lower at the highest dose and	Anonymous, 2004

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
	weaning of F1B pups F1: 75 D of premating period and until weaning of F2 pups	outside the range of HCD (10/00 – 06/02; Wistar rat) Duration of gestation: sign. higher at 500 mg/kg bw/d and outside the range of HCD (10/00 – 06/02; Wistar rat) Nb of females with liveborn pups decreased at the highest dose (17 F vs 24 F in control) Nb of females with stillborn pups increased at the highest dose (13 F** vs 5 F in control) Hormone examination: sign. decrease in ALD, CC, T, LH and FSH levels at the highest dose F1A pups: Mean nb of pups sign. decreased at the highest dose and outside the range of HCD (10/00 – 06/02; Wistar rat) At 500 mg/kg bw/d: sign. increased: nb of stillborn pups, nb of pups died and nb of pups cannibalized Viability index: 95, 100, 99 and 74 %, resp. at 0, 20, 100 and 500 mg/kg bw/d (HCD 96 to 100 %; (10/00 – 06/02; Wistar rat)) Survival index: 100 % in all groups Pups bw: sign. lower at the highest dose F0X and F0Y parents (doses: 0, 20, 100 and 300 mg/kg bw/d, 25, 25, 24, 25 animal per group): Mortality: 1 F in control sacrificed (unable to deliver) + 1 F at the highest dose found dead (necropsy: severe chronic nephropathy) Food cons.: reduced but not sign. Bw: sign. lower at the highest dose in M and F Male fertility: nb of sperms, morphology and motility: unaffected Male fertility index: 92, 92, 96 and 92%, resp. at 0, 20, 100 and 300 mg/kg bw/d 23 M per group succeeded to mate and have pregnant female Female fertility: estrous cycle length: increased but within the range of HCD (10/00 – 06/02; Wistar rat) 23 F per group became pregnant Female fertility index: 92, 92, 96 and 92 %, resp. at 0, 20, 100 and 300 mg/kg bw/d Duration of gestation: between 22.0 and 22.3 days Necropsy: FBW lower (sign. in M) Histology: focal necrosis in liver, diffuse hypertrophy in adrenal cortex, eosinophilic droplets in kidneys	

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
		F1B pups: Mean nb of pups: sign. lower at the highest dose (8.0* vs 10.5 in control group) At the highest dose: sign. increased nb of stillborn pups, pups died and pups cannibalized Between PND 1 to 4: 16 pups died at the highest dose (only 1 in control group). Lower viability index 90 % vs 100 in control (outside the range of HCD: 96 to 100 %; (10/00 – 06/02; Wistar rat)) Survival index: 100, 100, 99 and 99 %, resp. at 0, 20, 100 and 300 mg/kg bw/d Pups bw: sign. increased (more pronounced at the mid dose) Necropsy: tot. nb of pups with macroscopic findings: 7, 2, 3 and 9 pups, resp. at 0, 20, 100 and 300 mg/kg bw/d F1M and F1F parents: Mortality: 1 F of the control group sacrificed (necropsy: atrophy of ovary, oviducts and uterus) + 1 F of the lowest group sacrificed (necropsy: severe chronic nephropathy) Bw: no sign. difference Male fertility: nb, morphology and motility of sperms: not sign. affected (but % of motility outside of the range of HCD (10/00 – 06/02; Wistar rat) 3 M of the highest dose (out of 25) did not mate 2 M of the control group (out of 24) and 2 M of the highest dose mated but female did not become pregnant Male fertility index: 92, 100, 100 and 80 %, resp. at 0, 20, 100 and 300 mg/kg bw/d Female fertility: estrous cycle length: increased in low and high doses: 3.9, 4.3, 3.9 and 4.2 days, resp. at 0, 20, 100 and 300 mg/kg bw/d (within the range of HCD: 3.8 to 5.4 days; (10/00 – 06/02; Wistar rat)) Mean mating day until DPC: sign. higher at the highest dose Mean nb of implantation sites: sign. increased at the mid dose Female fertility index: unaffected: 92, 100, 100 and 91 %, resp. at 0, 20, 100 and 300 mg/kg bw/d Mean nb of PI loss: relatively low in all groups Mean duration of gestation: increased at the mid and high doses Nb of female with stillborn pups higher at the highest dose (7 F vs 2 F in control)	

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
		Necropsy: FBW slightly reduced in M, unaffected in F Some organ weights sign. modified Histology: increased inc of diffuse atrophy in adrenal cortex, central hypertrophy in liver and dilatation of uterus horn(s) and uterus atrophy F2 pups: Mean nb of pups slightly lower at the highest dose but not dose-related At the highest dose: sign. increased nb of stillborn pups, pups which died and pups cannibalized Between PND 1 to 4: 15 pups of the highest dose died Viability index: lower at the highest dose (89 % vs 99 % in control) Between PND 5 to 21, no pups died. Survival index was of 100 % in all groups Pups bw: no treatment-related modification Necropsy: macroscopic findings observed in 3 pups of the highest dose vs 1 pups in control group NOAEL (general toxicity): 20 mg/kg bw/d NOAEL (fertility): 100 mg/kg bw/d NOAEL (development): 100 mg/kg bw/d	
Repeated dose 28-day oral toxicity study Wistar rat 5/sex/group OECD TG 407 GLP	DMPP Purity: 99.4 % Oral (diet) 4 weeks Doses: 0, 1500, 3000 and 6500 ppm (corresp. to 0, 126.8, 215.7 and 510.4 mg/kg bw/d in M and to 0, 130.7, 255.4 and 488.7 mg/kg bw/d in F)	See results in Table 68	Anonymous, 2021
Repeated dose 28-day oral toxicity study Wistar rat 5/sex/group No OECD guideline	DMPP Purity: 97.1 % Oral (gavage) 4 w + additional groups (control and high dose) for 2 w of recovery period	See results in Table 68	Anonymous, 1997

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
followed GLP	Doses: 0, 20, 100 and 500 mg/kg bw/d		
Subchronic oral toxicity study Wistar rat 10/sex/group OECD TG 408 GLP	DMPP Purity: 97.1 % Oral (diet) 3 months Doses: 0, 200, 1000 and 5000 ppm (corresp. to 0, 13.6, 69.2 and 353.8 mg/kg bw/d in M and to 0, 16.5, 82.1 and 400.7 mg/kg bw/d in F)	See results in Table 68	Anonymous, 2003

No human data or other data available.

10.10.2 Short summary and overall relevance of the provided information on adverse effects on sexual function and fertility

In a two-generation reproductive toxicity study (Anonymous, 2004), performed following OECD TG 416, groups of 25 female and 25 male Wistar rats per group were given, by diet, the test substance at a concentration of 0, 20, 100 and 300 or 500 mg/kg bw/d.

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

The F1A generation pups were observed and examined until post-natal day 4 (day of standardization group) or post-natal day 21. Based on the high maternal toxicity as well as the high developmental toxicity in the highest dose group (500 mg/kg bw/d), all surviving F1A pups were killed on day 21 post-partum and examined without selecting any F1A pups for a second parental generation.

After that, a second F0 parental generation began with the same animals used for the first parental generation. This generation was named F0X for males and F0Y for females, and were given test substance at a concentration of 0, 20, 100 and 300 mg/kg bw/d. Animals received the test substance during a premating period of 10 weeks. Animals were remated, if possible with the same partner as for the first mating (as so-called F0M and F0F rats), to produce a second litter (F1B generation pups). After weaning of F1B pups, the F0 generation parental animals (F0X and F0Y) were sacrificed.

After weaning of the F1B pups, 25 males and 25 females per group were selected to be the F1 parental generation (designated as F1M for males and F1F for females). Animals were exposed to the test substance at a concentration of 0, 20, 100 or 300 mg/kg bw/d during a premating period of minimum 75 days. After this premating period, F1M and F1F were mated at a ratio of 1:1. The F1F were allowed to litter and rear their pups (F2 pups generation) until day 4 (standardization) or 21 after parturition. Shortly after weaning, the F1 parental generation were sacrificed.

For F0M and F0F parents:

During the study period, one male of the mid dose group was found dead on the study week 16. At necropsy, malignant oligodendroglioma in brain was observed. Furthermore, one female of this group was sacrificed in a moribund state on GD 22. This female exhibited clinical signs from GD 19 until her sacrifice (poor general

state, blood in bedding, vaginal haemorrhage, signs of anaemia and piloerection). Malignant lymphoma was noted at necropsy. Lower food consumption was observed at the highest dose (approx. - 7 % in males and in females during the premating period and - 13 % and - 26 % in females resp. during the gestation and lactation periods, compared to control group). Furthermore, as observed in Table 15 and Table 16, significantly reduced body weight was observed at the highest dose in both sexes.

Table 15: Mean body weight in males (in g)

Dose level (in mg/kg bw/d)	0	20	100	500
W 0	111.2	112.2	111.6	110.4
W 5	284.3	286.0	287.5	279.1
W 10	362.6	362.7	358.6	338.4* (- 6.67 %)
W 15	401.2	401.7	399.6	364.8** (- 9.07 %)
W 18	418.9	415.2	409.2	365.4** (- 12.77 %)
BWG W 0 to 18	307.7	303.0	297.4	255.0** (- 17.13 %)

Table 16: Mean body weight in females (in g)

Dose level (in mg/kg bw/d)		0	20	100	500	HCD range (10/00 – 06/02; Wistar rat)
Premating period	W 0	99.2	99.1	98.4	99.5	
	W 5	179.6	173.2	174.4	175.1	
	W 10	210.9	205.1	205.8	199.8* (- 5.2 %)	
	BWG W 0 to 10	111.8	105.9	107.3	100.3** (- 10.3 %)	
Gestation period	D 0	216.2	209.7	210.4	204.9	152.3 – 288.3
	D 7	237.1	230.7	229.8	219.9** (- 7.25 %)	174.6 – 320.4
	D 14	258.2	251.4	250.9	232.8** (- 9.84 %)	189.7 – 356.6
	D 20	305.9	302.4	297.9	276.6** (- 9.58 %)	220.4 – 413.3
	BWG D 0 to 20	89.6	92.7	87.5	71.7** (- 19.98 %)	
Lactation period	D 1	231.6	235.9	232.1	216.4* (- 6.56 %)	179.2 – 330.4
	D 4	242.4	245.1	243.5	221.9** (- 8.48 %)	184.8 – 328.5
	D 7	250.5	250.6	247.5	229.7** (- 8.3 %)	194.3 – 350.3
	D 14	262.9	261.6	262.6	239.3** (- 8.98 %)	204.2 – 353.0
	D 21	256.6	253.0	254.7	235.7** (- 8.14 %)	199.8 – 337.9
	BWG D 0 to 21	25.0	17.1	22.6	19.4 (- 22.4 %)	

Concerning male fertility parameters (see Table 17), 25 males per group were placed with females. Among these animals, 3 males of the highest dose did not mate. In total 8 males, exposed to this dose, failed to have pregnant female. When F0M and F0F were remated (renamed F0X and F0Y and exposed to 0, 20, 100 and 300 mg/kg bw/d), only 1 male of the mid dose and 1 male of the highest dose remained infertile. Sperm parameters were not examined.

Table 17: Male reproduction data

Dose level (in mg/kg bw/d)	0	20	100	500
Nb of males placed with females	25	25	25	25
Nb of males mated (male mating index in %)	25 (100 %)	25 (100 %)	25 (100 %)	22 (88 %)
Nb of males without pregnant females	1	0	1	8*
Male fertility index (in %)	96	100	96	68

Regarding female fertility parameters, mean days from estrous to estrous was significantly higher at the highest dose (4.0, 3.8, 3.9 and 4.8** days, resp. at 0, 20, 100 and 500 mg/kg bw/d). The mean mating day until DPC 0 was increased at the highest dose (see Table 18). At the highest dose, the female fertility index was decreased and outside the range of the HCD. When F0M and F0F were remated (renamed F0X and F0Y and exposed to 0, 20, 100 and 300 mg/kg bw/d), only 1 female of the mid dose and 1 female of the highest dose remained infertile. Furthermore, mean duration of gestation was also significantly increased at the highest dose and outside the range of the HCD (21.7 and 22.2 days), as it was of 21.9, 21.8, 21.8 and 22.6 days, resp. at 0, 20, 100 and 500 mg/kg bw/d

Table 18: Female reproduction data

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

At the end of the gestation period, the number of females with liveborn pups was decreased at the highest dose (24, 25, 23 and 17 females, resp. at 0, 20, 100 and 500 mg/kg bw/d). And the number of females with stillborn pups was significantly higher at this dose (5, 2, 2 and 13** females, resp. at 0, 20, 100 and 500 mg/kg bw/d).

F1 pups/litters: F1A pups

As observed in Table 19, the mean number of pups delivered was significantly reduced at the highest dose. The value of this dose was outside the range of the HCD. Furthermore, the number of stillborn pups, the number of pups which died and the number of cannibalized were significantly modified at the highest dose. Among the dams, 1 of the control group and 3 of the highest dose had total litter losses.

Table 19: Litter data

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

At the PND 1, the mean number of live pups per litter was severely reduced at the highest dose. The viability index was also modified, as it was of 95, 100, 99 and 74 %, resp. at 0, 20, 100 and 500 mg/kg bw/d. This reduction was outside the range of the HCD which was of 96 to 100 %. While the survival index was of 100 % in all dose groups.

Until weaning, pups body weight was examined and was significantly lower at the highest dose (see Table 20). The body weight change during PND 1 to 4 was slightly reduced at the highest dose, while between PND 4 and 21, pups body weight change was significantly decreased at this dose (see Table 21).

Table 20: Pups body weight (in g)

Dose level (in mg/kg bw/d)		0	20	100	500
PND 1	M	6.1	6.4	6.4	5.7
	F	5.7	6.0	6.0	5.2*
	M+F	5.9	6.2	6.2	5.3** (- 10.17 %)
PND 4 (preculling)	M	9.3	9.6	9.5	8.5
	F	9.0	9.2	9.0	8.1
	M+F	9.2	9.4	9.2	8.2* (- 10.87 %)
PND 4 (postculling)	M	9.3	9.7	9.5	8.5
	F	9.0	9.2	9.1	8.1*
	M+F	9.2	9.5	9.3	8.2* (- 10.87 %)
PND 7	M	14.9	15.1	14.8	12.1**
	F	14.4	14.5	14.3	11.6**
	M+F	14.7	14.8	14.6	11.8** (- 19.73 %)
PND 14	M	29.5	29.5	29.1	24.2**
	F	29.0	28.7	28.5	23.5**
	M+F	29.3	29.1	28.8	23.8** (- 18.77)
PND 21	M	47.5	47.5	47.0	39.4**
	F	46.0	46.1	45.8	38.5**
	M+F	46.8	46.8	46.4	38.9** (- 16.88 %)

Table 21: Pups body weight change (in g)

Dose level (in mg/kg bw/d)		0	20	100	500
PND 1 to 4	M	3.2	3.2	3.1 (-3.1 %)	2.8 (- 12.5 %)
	F	3.2	3.1	3.1 (-3.1 %)	2.7 (- 15.6 %)
	M+F	3.2	3.2	3.1 (-3.1 %)	2.8 (- 12.5 %)
PND 4 to 21	M	38.2	37.8	37.5 (-1.8 %)	30.9** (- 19.1 %)
	F	37.1	37.0	36.8 (-0.8 %)	30.4** (- 18.1 %)
	M+F	37.7	37.4	37.2 (-1.3 %)	30.6** (- 18.3 %)

At necropsy, total number of pups with findings was not modified compared to the control group. Three organs (brain, thymus and spleen) weights revealed significant modification at the highest dose (see Table 22). However, this change was within the range of HCD.

Table 22: Pups organ weight data (in g or %)

Dose level (in mg/kg bw/d)		0	20	100	500	HCD range (Oct 00 – Jun 02; Wistar rat)
Brain	Abs	1.465	1.479	1.474	1.422*	0.888 – 1.697
	Rela	3.148	3.162	3.211	3.699**	1.773 – 5.821
Thymus	Abs	0.216	0.219	0.216	0.177*	0.042 – 0.322

	Rela	0.462	0.467	0.470	0.459	0.198 – 0.662
Spleen	Abs	0.222	0.223	0.212	0.159**	0.027 – 0.392
	Rela	0.472	0.472	0.460	0.404**	0.136 – 0.741

For P adults: F0X and F0Y parents

At the beginning of this cohort, the number of animals was of 25 animals/sex/group (except for the mid dose which has 24 animals/sex).

During the study period, one female of the control group was sacrificed on GD 23. This female was unable to deliver completely and in poor general state (chromodacryorrhea, hypothermia and piloerection). Furthermore, one female of the highest dose was found dead during study week 17, her necropsy revealed severe chronic progressive nephropathy. The mean food consumption was not significantly modified but it was slightly lower at the highest dose. However, as observed in Table 23, body weight was significantly decreased at the highest dose in both sexes.

Table 23: Body weight (in g)

Dose level (in mg/kg bw/d)		0	20	100	300
Males					
W 0		418.1	418.8	411.0	359.6** (- 13.99 %)
W 5		440.0	436.1	431.2	392.4** (- 10.82 %)
W 10		452.8	453.3	445.9	408.4** (- 9.81 %)
W 15		462.6	462.5	457.7	418.7** (- 9.49 %)
W 17		471.0	468.3	464.0	425.6** (- 9.64 %)
BWG (W 0 to 17)		52.9	49.5	53.0	66.0* (+ 24.76 %)
Females					
Premating period	W 0	238.1	237.4	236.7	217.0** (- 8.86 %)
	W 5	243.2	239.5	236.4	226.9** (- 6.7 %)
	W 10	248.2	245.4	245.9	233.1* (- 6.09 %)
	BWG (W 1 to 10)	10.2	7.9	9.2	16.1* (+ 57.84 %)
Gestation period	D 0	248.6	246.8	245.0	231.6** (- 6.84 %)
	D 7	269.5	268.1	255.3	249.3** (- 7.5 %)
	D 14	288.2	288.2	283.1	262.2** (- 9.02 %)
	D 20	338.6	341.4	331.2	304.6**(- 10.04 %)
	BWG (D 0 to 20)	90.1	94.6	86.2	73.0** (- 18.98 %)
Lactation period	D 1	264.2	266.5	266.9	244.8** (- 7.34 %)
	D 4	273.8	278.4	273.3	252.3** (- 7.85 %)
	D 7	279.4	281.9	280.8	258.1** (- 7.62 %)
	D 14	286.5	293.3	287.9	264.8** (- 7.57 %)
	D 21	276.5	280.1	281.6	265.9 (- 3.83 %)
	BWG (D 1 to 21)	12.4	13.6	14.7	21.1 (+ 70.16 %)

Regarding male fertility, sperm parameters were examined. Number of sperms, morphology and motility did not reveal modifications and were within the range of the HCD (see Table 24). Among the mated males (25 in all groups, except at the mid dose 24 males), 23 males per group succeeded and females were pregnant.

Table 24: Sperm evaluation

Dose level (in mg/kg bw/d)	0	20	100	300	HCD range
Mean tot spermatids/g testis	120	NT	NT	117	94 - 144
Mean tot sperm/g cauda epididyma	585	NT	NT	562	517 – 727

Mean % normal sperm	98.1	NT	NT	97.6	94.8 – 99.1
Mean % abnormal sperm	1.9	NT	NT	2.4	0.9 – 5.2
Mean % motility	92	90	91	89	81 - 92

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

Concerning female fertility, cycle length was increased at the highest dose, however the increase was within the range of the HCD (4.1, 4.0, 4.1 and 4.9 days, resp. at 0, 20, 100 and 300 mg/kg bw/d ; HCD (10/2000 – 01/2002 (Wistar rat): 3.8 to 5.4 days). Among mated females (25 per group, except for the mid dose 24 females), 23 females per group became pregnant. Mean mating day until DPC 0 was not modified, as it was of 2.8, 2.9, 2.5 and 3.0 days, resp. at 0, 20, 100 and 300 mg/kg bw/d. Based on these results, female fertility index was of 92, 92, 96 and 92 %, resp. at 0, 20, 100 and 300 mg/kg bw/d. Duration of gestation was similar in all groups (between 22.0 and 22.3 days). At the end of the gestation period, 21, 23, 23 and 21 females had liveborn pups, while 1 female of the control group and 2 females of the highest dose had all stillborn pups (see Table 25).

Table 25: Number of pups

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

After pups weaning, animals were sacrificed. Necropsy did not reveal any treatment-related macroscopic findings. However, final body weight was significantly lower in males exposed to the highest dose, while in females the decrease was not significant. In males, adrenal glands, brain, kidneys, liver, pituitary and spleen exhibited significant weights changes. Furthermore, as observed in Table 26, absolute prostate weight was reduced at 300 mg/kg bw/d (approx. - 31 % compared to the control group). While relative prostate weight was only slightly reduced at this dose. Relative seminal vesicle and testes weight showed also significant modifications at the highest dose. In females, adrenal glands, brain and kidneys weights were modified at the highest dose as well as absolute ovaries weight. Microscopic examination revealed a higher incidence of liver hypertrophy in males, of adrenal cortex diffuse hypertrophy in both sexes, of eosinophilic droplets in kidneys in males (see Table 27). While reproductive organs examination did not show any treatment-related modification.

Table 26: Organ weight (in mg, g or %)

		Males				Females			
Dose level (in mg/kg bw/d)		0	20	100	300	0	20	100	300
FBW (g)		435.904	434.368	431.667	395.304*	239.146	236.408	237.625	226.05
Adrenal glands (mg)	Abs	56.56	56.32	58.333	66.92**	73.583	75.56	75.292	85.25
	Rela	0.013	0.013	0.014	0.017**	0.031	0.032	0.032	0.038**
Brain (g)	Abs	2.072	2.095	2.076	2.073	1.906	1.931	1.92	1.92
	Rela	0.48	0.487	0.483	0.529**	0.802	0.819	0.809	0.853**
Kidneys (g)	Abs	2.483	2.515	2.543	2.888**	1.749	1.768	1.803	1.805
	Rela	0.571	0.582	0.59	0.732**	0.734	0.749	0.759	0.8**
Liver (g)	Abs	10.143	10.209	10.362	10.306	6.617	6.722	6.706	6.429
	Rela	2.327	2.351	2.4	2.604**	2.766	2.841	2.821	2.835
Pituitary gland (mg)	Abs	9.68	9.64	10.083	10.04	13.208	12.64	14.083	18.917
	Rela	0.002	0.002	0.002	0.003**	0.006	0.005	0.006	0.008
Spleen (g)	Abs	0.75	0.747	0.713	0.746	0.537	0.54	0.578	0.515
	Rela	0.173	0.173	0.166	0.189*	0.226	0.229	0.244	0.229

Thyroid glands (mg)	Abs	22.44	21.88	21.542	21.68	16.5	15.64	15.167	17.5
	Rela	0.005	0.005	0.005	0.006	0.007	0.007	0.006	0.008
Cauda epididymides (g)	Abs	0.473	0.456	0.463	0.427	-	-	-	-
	Rela	0.109	0.105	0.108	0.108	-	-	-	-
Epididymides (g)	Abs	1.192	1.173	1.161	1.102	-	-	-	-
	Rela	0.275	0.272	0.27	0.279	-	-	-	-
Prostate (g)	Abs	1.135	1.078	1.025	0.774**	-	-	-	-
	Rela	0.263	0.249	0.239	0.253	-	-	-	-
Seminal vesicle (g)	Abs	1.002	0.999	1.025	0.997	-	-	-	-
	Rela	0.231	0.232	0.239	0.196*	-	-	-	-
Testes (g)	Abs	3.806	3.827	3.686	3.735	-	-	-	-
	Rela	0.876	0.887	0.859	0.947*	-	-	-	-
Ovaries (mg)	Abs	-	-	-	-	105.917	103.28	113.125	93.792*
	Rela	-	-	-	-	0.045	0.044	0.048	0.042
Uterus (g)	Abs	-	-	-	-	0.718	0.732	0.648	0.702
	Rela	-	-	-	-	0.302	0.31	0.273	0.314

Table 27: Microscopic findings

		Males				Females			
Dose level (in mg/kg bw/d)		0	20	100	300	0	20	100	300
Adrenal cortex									
Nb animals examined		25	2	2	25	25	2	2	25
Diffuse hypertrophy		0	0	0	20 (grade 2)	0	0	0	20 (grade 1)
Kidneys									
Nb animals examined		25	3	2	25	25	2	2	25
Calcification, medulla		1	0	0	0	6	0	0	11
Calcification, pelvis		3	0	0	4	10	1	0	11
Calcification, papilla		2	0	0	0	2	0	0	1
Nephropathy		4	0	0	7	4	0	1	7
Eosinophilic droplets	Inc	4	0	0	9	0	0	0	0
	Grade 1	4	-	-	5	-	-	-	-
	Grade 2	-	-	-	4	-	-	-	-
Liver									
Nb animals examined		25	2	2	25	0	1	0	1
Focal necrosis		1	0	0	1	-	-	-	-
Central hypertrophy	Inc	0	0	0	23	-	-	-	-
	Grade 1	-	-	-	17	-	-	-	-
	Grade 2	-	-	-	6	-	-	-	-
Spleen									
Nb animals examined		25	2	2	25	-	-	-	-
Hematopoiesis		20	1	1	22	-	-	-	-
Epididymis, left									
Nb animals examined		25	2	2	25	-	-	-	-
Lymphoid infiltr.		2	0	0	4	-	-	-	-
Testes, left									
Nb animals examined		25	2	2	25	-	-	-	-
Degeneration, focal		3	0	1	3	-	-	-	-
Degeneration, diffus		0	0	0	1	-	-	-	-
Prostate									

Nb animals examined	25	2	2	25	-	-	-	-
Inflamm. chronic	7	0	0	7	-	-	-	-
Uterus								
Nb animals examined	-	-	-	-	25	2	2	25
Dilation of horn(s)	-	-	-	-	9	1	0	4

For F1 pups/litters: F1B pups

At delivery, mean number of pups was significantly lower at the highest dose. Moreover, as observed in Table 28, total number of liveborn and stillborn pups, as well as number of pups which died and which were cannibalized were significantly changed.

Table 28: Number of pups

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

Between PND 1 to 4, 16 pups of the highest dose died compared to only 1 in control group. This observation results in a lower viability index at this dose (100, 99, 100 and 90 %, resp. at 0, 20, 100 and 300 mg/kg bw/d) and this decrease was outside the range of HCD which was comprised between 96 to 100 %. After this higher mortality rate, between PND 5 to 21, only 2 pups of the highest dose died and results in a survival index at weaning of 100, 100, 99 and 99 %, resp. at 0, 20, 100 and 300 mg/kg bw/d.

Pups body weight was examined until weaning and showed significant modification but only at 100 mg/kg bw/d. Furthermore, all the data were within the range of the HCD (see Table 29).

Table 29: Pups body weight (in g)

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

At necropsy, total number of pups with findings was only of 7, 2, 3 and 9 pups, resp. at 0, 20, 100 and 300 mg/kg bw/d. Moreover, brain, thymus and spleen were weighed. Significant changes were observed, however, these were not dose-related.

For F1 adults: F1M and F1F parents

At the beginning of this generation, 25 rats per sex per dose were used. One female of the control group was sacrificed during the study week 8. This female had only half of the body weight of the other control females, had still not opened its vagina and did not develop upper incisive. Her necropsy revealed distinct atrophy of ovary, oviducts and uterus. Moreover, one female of the lowest dose group was sacrificed in a moribund state during study week 10 (poor general state, apathy, piloerection and red crust formation at its nose). Her necropsy revealed a severe chronic progressive nephropathy. As observed in Table 30 and Table 31, body weight examination did not reveal significant modification.

Table 30: Body weight in males (in g)

Dose level (in mg/kg bw/d)	0	20	100	300
W 1	71.4	75.5	78.0	69.7 (- 2.38 %)
W 5	258.5	272.5	271.1	258.9 (+ 4.87 %)
W 10	345.4	365.6	359.5	343.7 (- 0.49 %)
W 14	378.8	394.5	386.5	367.2 (- 3.06 %)
W 17	397.7	414.9	407.9	384.0 (- 3.44 %)
BWG (W 0 to 17)	326.2	339.4	330.0	314.3 (- 3.65 %)

Table 31: Body weight in females (in g)

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

As observed in Table 32, biochemical examination showed significant modification of ALT and GLDH. Furthermore, some hormones were examined and revealed also significant changes.

Table 32: Biochemical and hormonal examination

	Males				Females			
Dose level (in mg/kg bw/d)	0	20	100	300	0	20	100	300
ALT (µkat/L)	0.75	0.68	0.81	0.85**	0.70	0.65	0.60*	0.61*
AST (µkat/L)	2.56	2.17	2.45	2.52	2.24	2.13	191	2.03
ALP (µkat/L)	1.18	1.21	1.18	1.15	0.71	0.72	0.71	0.74

SGGT (nkat/L)	5	3	6	5	9	7	7	9
GLDH (nkat/L)	140	173*	209**	236**	130	97	129	191**
Tot. prot. (g/L)	70.81	70.19	71.15	71.08	68.0	68.67	68.12	70.47
Chol (mmol/L)	2.03	2.12	2.27*	2.92**	1.52	1.38	1.37	1.84**
ALD (pmol/L)	711.55	658.71	538.38*	561.86	1953.93	1894.92	1857.95	1305.03**
CC (nmol/L)	776.36	588.61	526.70	664.15	2508.74	2313.71	2258.12	1970.37*
T (nmol/L)	7.57	7.17	3.33*	3.28	1.26	1.24	1.10	0.81*
LH (µg/L)	1.26	0.99	0.97	1.08	20.29	15.49	35.53	21.12
FSH (µg/L)	11.68	11.97	12.00	11.79	10.89	9.87	10.27	13.24
E_2 (pmol/L)	-	-	-	-	199.67	179.39	142.99*	106.97**

Regarding male reproductive parameters, number, morphology and motility of sperms were not significantly affected. Mean percentage of motility was lower and outside the range of HCD at the highest dose, however, the percentage was decreased of approx. 8 % compared to the control group. Among males placed with females (24 in control and low doses and 25 at the mid and high doses), 3 males of the highest dose did not mate. Furthermore, 2 males of the control group and 2 males exposed to 300 mg/kg bw/d did not become pregnant.

Table 33: Sperm evaluation and male cohabitation data

Dose level (in mg/kg bw/d)	0	20	100	300	HCD range
Mean tot spermatids/g testis	121	NT	NT	125	94 - 144
Mean tot sperm/g cauda epididyma	594	NT	NT	532	517 – 727
Mean % normal sperm	98.0	NT	NT	95.7	94.8 – 99.1
Mean % abnormal sperm	2.0	NT	NT	4.3	0.9 – 5.2
Mean % motility	84	82	86	77	81 - 92
Nb of males placed with females	24	24	25	25	
Nb of males mated	24	24	25	22	
Nb of males with females pregnant	22	24	25	20	
Male fertility index (in %)	92	100	100	80	

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

Concerning female reproductive parameters, estrous cycle length was increased at the low and high doses and was of 3.9, 4.3, 3.9 and 4.2 days, resp. at 0, 20, 100 and 300 mg/kg bw/d. Furthermore, these modifications were within the range of the HCD (3.8 – 5.4 days). Among 24 mated females per group (except at the highest dose: 22 mated females), 22, 24, 25 and 20 females per group were pregnant, resp. at 0, 20, 100 and 300 mg/kg bw/d. As observed in Table 34, mean mating until DPC 0 was significantly higher at the highest dose. While the mean number of implantation sites was significantly increased at the mid dose (10.6, 10.7, 12.2* and 10.5, resp. at 0, 20, 100 and 300 mg/kg bw/d). However, female fertility index was unaffected by treatment, as it was of 92, 100, 100 and 91 %, resp. at 0, 20, 100 and 300 mg/kg bw/d.

Table 34: Female reproduction data

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

During the gestation period, mean number of post-implantation loss was relatively low in all groups (0.5, 0.7, 1.4 and 0.9, resp. at 0, 20, 100 and 300 mg/kg bw/d).While mean duration of gestation was increased at the mid and high doses and the modification was significant at the highest dose (21.5, 21.5, 21.8 and 22.0 days, resp. at 0, 20, 100 and 300 mg/kg bw/d). At the end of the gestation period, number of females with liveborn pups was similar between the control and the highest dose, as it was of 21, 24, 25 and 20 dams, resp. at 0, 20, 100 and 300 mg/kg bw/d. However, as observed in Table 35, the number of females with stillborn pups was increased at the highest dose.

Table 35: Number of liveborn and stillborn pups

Dose level (in mg/kg bw/d)	0	20	100	300
Number of females with liveborn pups	21	24	25	20
Number of females with stillborn pups	2	1	1	7
Number of females with all stillborn pups	0	0	0	0
Mean number of pups delivered	10.6	10.0	10.8	9.6

After weaning, animals were sacrificed and examined. Their necropsy did not reveal any treatment-related macroscopic findings. Final bodyweight was unaffected by treatment in females while it showed slight variations in males. Furthermore, as observed in Table 36, few organ weights were significantly modified. These effects were more pronounced in males. Regarding reproductive organs, absolute seminal vesicle weight was significantly lower at the highest dose (approx. -15 % compared to control group). Relative weight was not significantly modified but showed a slight decrease (approx. -12 % compared to control group). In females, ovaries weight was significantly higher at the mid dose while the weight at the highest dose was slightly lower.

Table 36: Organ weight data (in mg, g or %)

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

	Rela	1.012	1.0	0.986	0.997	-	-	-	-
Ovaries (mg)	Abs	-	-	-	-	107.75	168.833[A]	119.36*	102.8
	Rela	-	-	-	-	0.049	0.075	0.053	0.047
Uterus (g)	Abs	-	-	-	-	0.6	0.608	0.677	0.695
	Rela	-	-	-	-	0.273	0.274	0.301	0.318

[A]: St. Dev.: 289.166

Microscopic examination revealed an increased incidence of diffuse hypertrophy in adrenal cortex as this was observed in 18 males and 21 females exposed to 300 mg/kg bw/d. Moreover, central hypertrophy in liver was also noted only at the highest dose, in 18 males and 16 females. Dilatation of the uterus's horn(s) was observed in 11 females exposed to 300 mg/kg bw/d compared to only 4 females of the control group. Furthermore, uterus atrophy was observed in 3 females of the highest dose and only in 1 female of the control group.

For F2 pups/litters:

At delivery of the F2 generation, mean number of pups per dams was slightly lowered at the highest dose, however the change was not dose-related, as it was of 10.6, 10.0, 10.8 and 9.6 pups per dams, resp. at 0, 20, 100 and 300 mg/kg bw/d. As observed in Table 37, total number of liveborn pups, stillborn pups, pups which died and the number of pups which were cannibalized were significantly changed at the highest dose.

Table 37: Number of pups

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

During the observation period, 15 pups of the highest dose died between PND 1 to 4. The viability index was then reduced at the highest dose, as it was of 89 % compared to 99 % in control group. Between PND 5 to weaning, as no pups died at the highest dose, the survival index was of 100 %. Furthermore, pups body weight examination did not exhibit treatment-related change (see Table 39).

Table 38: Pups mortality data

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

Table 39: Pups body weight (in g)

Dose level (in mg/kg bw/d)		0	20	100	300	HCD range
PND 1	M	6.0	6.3	6.3	6.0	4.9 – 8.5
	F	5.7	6.0	6.0	5.8	4.5 – 7.9
	M+F	5.8	6.1	6.2	5.9	4.7 – 7.9
PND 4 (preculling)	M	9.2	9.6	9.4	9.4	
	F	8.8	9.4	9.1	9.2	
	M+F	9.0	9.5	9.2	9.3	

PND 4 (postculling)	M	9.2	9.7	9.5	9.4	
	F	8.9	9.4	9.1	9.2	
	M+F	9.1	9.5	9.3	9.3	
PND 7	M	14.9	15.2	15.0	14.7	8.6 – 19.9
	F	14.6	14.8	14.5	14.5	6.7 – 18.7
	M+F	14.7	14.9	14.8	14.6	7.3 – 19.0
PND 14	M	29.7	30.1	29.5	29.5	15.3 – 38.8
	F	29.4	29.3	28.7	29.3	10.1 – 36.5
	M+F	29.6	29.6	29.1	29.4	12.7 – 37.3
PND 21	M	46.5	47.5	47.3	47.3	22.9 – 61.9
	F	45.9	46.1	45.7	46.7	17.7 – 58.3
	M+F	46.3	46.7	46.5	47.0	20.3 – 60.1

At pups necropsy, only 3 pups of the highest dose had findings which were not treatment-related, compared to 1 pup in the other groups. Brain, thymus and spleen were weighed and did not show modifications (see Table 40).

Table 40: Pups organ weight (in g or %)

Dose level (in mg/kg bw/d)		0	20	100	300	HCD range (Oct 00 – Jun 02)
Brain	Abs	1.465	1.479	1.479	1.493	0.888 – 1.697
	Rela	3.171	3.165	3.203	3.202	1.773 – 5.821
Thymus	Abs	0.222	0.217	0.224	0.222	0.042 – 0.322
	Rela	0.479	0.462	0.483	0.471	0.198 – 0.662
Spleen	Abs	0.218	0.225	0.220	0.225	0.303 – 0.538
	Rela	0.479	0.473	0.471	0.474	0.136 – 0.741

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

Two 28-days and one 90-day repeated dose toxicity studies were available. The results are described in section 10.12.1 of this CLH dossier.

10.10.3 Comparison with the CLP criteria

Table 41: Comparison with CLP criteria regarding fertility

CLP criteria for a classification as Repr. Cat. 1	CLP criteria for a classification as Repr. Cat. 2
Known or presumed human reproductive toxicant Substances are classified in Category 1 for reproductive toxicity when they are known to have produced an adverse effect on sexual function and fertility, or on development in humans or when there is evidence from animal studies, possibly supplemented with other information, to provide a strong presumption that the substance has the capacity to interfere with reproduction in humans. The classification of a substance is further distinguished on the basis of whether the evidence for classification is primarily from human data (Category 1A) or from animal data (Category 1B).	Suspected human reproductive toxicant Substances are classified in Category 2 for reproductive toxicity when there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development, and where the evidence is not sufficiently convincing to place the substance in Category 1. If deficiencies in the study make the quality of evidence less convincing, Category 2 could be the more appropriate classification. Such effects shall have been observed in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction

Category 1A: Known human reproductive toxicant The classification of a substance in this Category 1A is largely based on evidence from humans. Category 1B: Presumed human reproductive toxicant The classification of a substance in this Category 1B is largely based on data from animal studies. Such data shall provide clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary nonspecific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate.	is considered not to be a secondary non-specific consequence of the other toxic effects.

Since no human studies are available for effects on fertility, a classification as Repr. 1A for fertility is not appropriate.

- **Male fertility:**

In the available two-generation reproductive toxicity study (Anonymous, 2004), F0 parental generation was initially exposed to 0, 20, 100 and 500 mg/kg bw/d. 3 males exposed to the highest dose (out of 25) did not mate. Furthermore, in total, 8 males failed to have female pregnant. At the next step of the study, when the highest dose was reduced to 300 mg/kg bw/d, only 1 male exposed to this dose remained infertile. In this part of the study, sperm parameters were examined and did not reveal significant modification or data outside the range of the HCD.

In the F1 parental generation, the same effect was observed, as 3 males exposed to 300 mg/kg bw/d failed to mate and 2 males which mated failed to have a pregnant female. In this generation, sperm parameters were examined. No significant difference was noted, however sperm motility was reduced at the highest dose and outside the range of HCD, even if the change was not dose-related.

Table 42 : Summary table of male fertility in the two-generation reproductive toxicity study (Ano., 2004)

Dose level (in mg/kg bw/d)	0	20	100	300	500
F0M	No effects	No effects	No effects	/	Among 25 males examined : 3 M not mated and In total 8 M failed to have female pregnant
F0Y	No effects	No effects	No effects	1 M remained infertile	/
F1M	No effects	No effects	No effects	3 M not mated 2 M mated but female not pregnant	/

In the F0 and F1 parental generation, no treatment-related mortality was observed as well as no treatment-related clinical signs. In the F0 generation, a statistically significant decreased body weight was noted at the highest dose. In the F0M, the decrease was of approx. - 6 to - 17 % compared to control group. In the second step of the F0 generation, when the highest dose was reduced to 300 mg/kg bw/d, body weight at W0 was lowered of - 13.99 % while it was only reduced of - 9.64 % at the end of the exposure period, which result in a BWG (W0 to 17) statistically significantly higher (+ 24.76 % compared to control group). In the F1 generation, body weight in males was not significantly reduced during the study period and the BWG was only reduced to - 3.65 % compared to the control group.

Even if the general state seems to be better in the F1 parental generation, the same effect was observed as 3 males of the highest dose did not mate and 2 males mated but failed to have a pregnant female. Then 5 males out of 25 did not succeed to have a female pregnant.

After weaning of the F1B pups, parental males of the F0 generation were necropsied and male reproductive organ were examined and revealed several weights change. Absolute prostate weight was significantly reduced at the highest dose, while relative weight was similar. Seminal glands weight examination exhibited also modification, as relative weight was significantly lowered at the highest dose (absolute weight was similar). Testes weight was also affected, relative weight was significantly higher and absolute weight was unaffected.

Parental males of the F1 generation, absolute seminal vesicle weight was significantly lower, while relative weight was reduced but not significantly. Other male reproductive organ did not show significant modification.

In the available repeated dose toxicity studies (two 28-day and one 90-day), male reproductive organ weight were examined.

In the 28-day repeated dose toxicity study (Anonymous, 2021), absolute and relative prostate weights were reduced at the highest dose (absolute weight: approx. - 12.54 % compared to control group and relative weight: approx. - 11.21 % compared to the control group).

In the second 28-day repeated dose toxicity study (Anonymous, 1997), epididymis weight was unaffected at the end of the exposure period, while it was significantly reduced at the highest dose at the end of the recovery period (absolute and relative weights).

In the subchronic toxicity study (Anonymous, 2003), male reproductive organ weights (epididymis and testes) were examined and did not show treatment-related modification.

- **Female fertility:**

In the available two-generation reproductive toxicity study (Anonymous, 2004), few parameters were disrupted by the treatment. As observed in Table 43, estrous cycle length was higher at the highest dose in the F0 and F1 generation. The modification was more pronounced in the F0 generation. Mean mating day until DPC was also increased at the highest dose in both generation. In the F0F, mean mating day was of 3.5, this data was just below the upper limit of the HCD. In the F0F generation, fertility index was reduced at the highest dose (77 % vs 96 % in control) and this value was outside the range of HCD.

Table 43: Summary of female fertility parameters

Dose level (in mg/kg bw/d)		0	20	100	300	500	HCD
Estrous cycle length (in day)	F0F	4.0	3.8	3.9	/	4.8**	
	F0Y	4.1	4.0	4.1	4.9	/	3.8 – 5.4
	F1F	3.9	4.3	3.9	4.2	/	
Mean mating day until DPC (in day)	F0F	2.8	2.7	2.3	/	3.5	2.1 – 3.6
	F0Y	2.8	2.9	2.5	3.0	/	
	F1F	2.1	2.0	2.5	3.1*	/	
Female fertility index (in %)	F0F	96	100	96	/	77	84 – 100 %

	F0Y	92	92	96	92	/	
	F1F	92	100	100	91	/	

Furthermore, three studies examined the duration of gestation. In all of them, this parameter was affected by the treatment. In the F0 of the two-generation reproductive toxicity (Anonymous, 2004), duration of gestation was increased at the highest dose (500 mg/kg bw/d) and outside the range of HCD. When the dose was reduced to 300 mg/kg bw/d in F0 generation, duration of gestation is similar in all groups. While at the F1 generation, a dose-related increase was noted and the duration was significantly increased at the highest dose (300 mg/kg bw/d). In the pre- and post-natal developmental toxicity study (Anonymous, 2013), the modification of duration of gestation was slightly higher at the highest dose (300 mg/kg bw/d) and the change was dose-related. Furthermore, a toxicity study concerning the influence of DMPP on the phosphate metabolism of adults rats and suckling pups demonstrated a significantly increased duration of gestation at 500 mg/kg bw/d compared to control group.

Table 44: Summary table of effects on the duration of gestation

Dose level (in mg/kg bw/d)		0	20	25	80	100	300	320	400	500	HCD
Two-gen (Ano., 2004)	F0F	21.9	21.8	/	/	21.8	/	/	/	22.6	21.7 – 22.2
	F0Y	22.2	22.0	/	/	22.2	22.3	/	/	/	
	F1F	21.5	21.5	/	/	21.8	22.0*	/	/	/	
Pre- and postnatal study (Ano., 2013)		21.9	22.0	/	/	22.1	22.3	/	/	/	
Toxicity study (Ano, 2017)		22.3	/	/	/	/	/	/	/	22.8*	

In the available repeated dose toxicity studies, female reproductive organs (ovaries and uterus) were examined and did not exhibit treatment-related modification.

- **<u>Conclusion regarding fertility:</u>**

In the available two-generation reproductive toxicity study (Anonymous, 2004), in both generations, several females failed to become pregnant. Female fertility index was then decreased and was outside the range of HCD when animals were exposed to 500 mg/kg bw/d. Furthermore, fertility parameters such as estrous cycle and mean mating day until DPC were affected by treatment. At necropsy, no macroscopic or microscopic treatment-related change was observed in the female reproductive organ.

Furthermore, in this two-generation reproductive toxicity study (Anonymous, 2004), several males failed to mate or mate but failed to have a female pregnant. Moreover, male reproductive organ weights exhibited modification.

In conclusion, DS is of the opinion that a classification for fertility is warranted as **Repr. 1B; H360F**.

10.10.4 Adverse effects on development

Table 45: Summary table of animal studies on adverse effects on development

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
Two-generation reproductive toxicity study Rat (Wistar)	DMPP Purity: 97 % Conc.: 0, 20, 100 and 500/300	See Results in Table 14	Anonymous, 2004

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
25/sex/group OECD TG 416 GLP	mg/kg bw/d Duration of exposure: F0 generation: 75 D before mating for M and F and until LD 21 for F. F1A pups (examined until PND 4 or 21) Second F0 generation (with same animals): 10 week premating and until weaning of F1B pups F1: 75 D of premating period and until weaning of F2 pups		
Pre- and postnatal developmental toxicity study (Range-finding study) Rat (Wistar) 25/group OECD TG 416 GLP	DMPP Purity: 99.4 g/100g Conc.: 0, 20, 100 and 300 mg/kg bw/d Duration of exposure: GD 6 to weaning of pups	Dams: No mortality during the study period No treatment-related clinical sign Bw: no sign. modification Hormone analysis: 11-deoxy-corticosterone: sign. and dose-related decrease. Sign. modification also for progesterone, corticosterone and 18-deoxy-corticosterone Mean duration of gestation: slightly higher (21.9, 22.0, 22.1 and 22.3 days, resp. at 0, 20, 100 and 300 mg/kg bw/d, within the range of HCD) Mean % of PI loss: 5.4, 4.4, 6.4 and 6.8 %, resp. at 0, 20, 100 and 300 mg/kg bw/d (within the range of HCD) Nb of female with liveborn pups: 24, 25, 23 and 24, resp. at 0, 20, 100 and 300 mg/kg bw/d Nb of female with stillborn pups: 0, 1, 1 and 2, resp. at 0, 20, 100 and 300 mg/kg bw/d Necropsy: no treatment-related macroscopic findings Histology: NE Fetuses: Mean nb of pups delivered: 10.5, 9.1, 9.4 and 9.3, resp. at 0, 20, 100 and 300 mg/kg bw/d Mortality between PND 1 to 4: 2, 1,	Anonymous, 2013

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
		2 and 16 pups died, resp. at 0, 20, 100 and 300 mg/kg bw/d Viability index: 99, 99, 99 and 92 %, resp. at 0, 20, 100 and 300 mg/kg bw/d Survival index: 99 % in control group and 100 % in all treated groups Pups bw: sign increased at the mid dose Tot nb of pups with necropsy findings: 10, 15, 14 and 8 pups, resp. at 0, 20, 100 and 300 mg/kg bw/d	
Prenatal toxicity study Rat (Wistar) 25/group OECD TG 414 GLP	DMPP Purity: 97.1 % Conc.: 0, 25, 100 and 400 mg/kg bw/d Duration of exposure: GD 6 to 15	Dams: No mortality during the study period At the highest dose: 12 F (out of 25): transient excessive salivation after exposure Bw: unaffected No female with abortion or premature birth % of PI loss: 11.5, 6.3, 9.0 and 11.3 %, resp. at 0, 25, 100 and 400 mg/kg bw/d Necropsy: no treatment-related macroscopic findings Histology: NE Net weight change: not sign. modified Fetuses: Mean nb of live fetuses: 12.8, 13.7, 12.7 and 12.7, resp. at 0, 25, 100 and 400 mg/kg bw/d Mean placental and fetal weights: not sign. modified External malformation: one fetus of the mid dose had anophthalmia Soft tissue observation: one fetus of the mid group: hydrocephaly and dilatation of both ventricles Skeletal observations: 1, 3, 0 and 5 pups exhibited malformation	Anonymous, 1997
Prenatal developmental	DMPP	Dams:	Anonymous,

Method, guideline, deviations if any, species, strain, sex, no/group	**Test substance, dose levels duration of exposure**	**Results**	**Reference**
toxicity study Rabbit (Himalayan) 5/group GLP	Purity: 97 % Conc.: 0, 25, 100 and 400 mg/kg bw/d Duration of exposure: GD 6 to 28	At the highest dose, all F sacrificed in a moribund state (at GD 14-15) Clinical signs: At 400 mg/kg bw/d: lateral position, apathy, poor general state, hypothermia, no defecation At 100 mg/kg bw/d: reduced defecation in all F Bw: sign. reduced in F of the highest dose at GD14 Higher pre- and post-implantation loss at the mid dose Fetuses: Mean nb of live fetuses: 7.5, 8.0 and 5.0, resp. at 0, 25 and 100 mg/kg bw/d Placental and fetal weight: unaffected No treatment-related malformation or variation	2007
Prenatal toxicity study Rat (Wistar) 10/group OECD TG 414 No info about GLP compliance	3,4-dimethylpyrazole phosphate Purity: unspecified Conc. 0, 20, 80 and 320 mg/kg bw/d Duration of exposure: GD 6 to 15	Dams: No mortality during the study period No treatment-related clinical signs Bw: not sign. modified % of PI loss and mean nb of resorption: lowered in all dose groups Nb of dams with viable fetuses: 9 in control and 10 in tested groups Necropsy: no treatment-related findings (histology NE) Net weight change: not sign. modified Fetuses: Mean nb of live births: 13.7, 12.6, 14.4 and 14.5, resp. at 0, 20, 80 and 320 mg/kg bw/d Placental weight and fetal weight unaffected External observation: no malformation or variation Soft tissue observation: increased inc. of variation (dilated renal	Anonymous, 1996

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
		pelvis and hydroureter) Skeletal observation: increased inc. of variation (irregular shape of sternebra, sternebra bipartite, 13th ribs shortened)	
Toxicity study concerning the influence of DMPP on the phosphate metabolism of adults rats and suckling pups	DMPP Purity: 99.4 g/100 g Conc.: 0 or 500 mg/kg bw/d Positive control group: calcitriol Duration of exposure: 10 w of premating period, max 14 d of mating period, during gestation and lactation period	No treatment-related mortality Clinical observations: during lactation period, 3 complete litter loss and 1 other not properly nursed Bw: sign. lowered at 500 mg/kg bw/d (from GD 7 to LD 14) Precoital interval: 3.3 and 3.5, resp. at 0 and 500 mg/kg bw/d (3.9 in PC) % of PI loss: 12 and 20 %, resp. at 0 and 500 mg/kg bw/d (17 % in PC) Duration of gestation: 22.3 and 22.8* days, resp. at 0 and 500 mg/kg bw/d (22.2 in PC) Fetuses: Mean nb of liveborn pups: 10 and 6, resp. at 0 and 500 mg/kg bw/d (11 in PC) Live birth index: 99.3 and 76.0 %, resp. at 0 and 500 mg/kg bw/d (98.6 % in PC) Nb of pups found dead: 0 and 8, resp. at 0 and 500 mg/kg bw/d Nb of pups cannibalized: 0 and 4, resp. at 0 and 500 mg/kg bw/d Pups bw: sign. reduced at 500 mg/kg bw/d	Anonymous, 2017

No human data or other data available.

10.10.5 Short summary and overall relevance of the provided information on adverse effects on development

In a two-generation reproductive toxicity study (Anonymous, 2004), performed following OECD TG 416, groups of 25 female and 25 male Wistar rats per group were given, by diet, the test substance at a concentration of 0, 20, 100 and 300 or 500 mg/kg bw/d.

Methods and results are described in section 10.10.2.

In a pre- and post-natal developmental toxicity study, range-finding study (Anonymous, 2013), performed according to OECD TG 416, groups of 25 pregnant female Wistar rats were exposed to the test

substance at a concentration of 0, 20, 100 and 300 mg/kg bw/d. Animals received daily DMPP from gestation day 6 until weaning of pups.

For Parental generation:

During the study period, no mortality occurred and no treatment-related clinical signs were observed. Between gestation day 6 and 13, mean food consumption was significantly reduced at the highest dose (20.0, 19.3, 19.7 and 17.4** g/animal/day, resp. at 0, 20, 100 and 300 mg/kg bw/d). As observed in Table 46, body weight examination did not show any modification.

Table 46: Body weight (in g)

Dose level (in mg/kg bw/d)		0	20	100	300	HCD range of actual values (01/07 to 02/11)
Gestation period	GD 0	169.1	166.8	167.4	167.5	172.7 – 298.9
	GD 6	201.8	198.3	199.4	199.7	At GD 7: 188.7 – 331.3
	GD 13	231.9	226.6	231.3	222.0	At GD 14: 207.7 – 350.3
	GD 20	291.0	279.5	289.0	285.2	225.6 – 418.3
	BWG GD 0 to 20	121.9	112.7	121.6	117.7	
Lactation period	LD 1	226.1	221.0	226.1	224.0	180.8 – 331.3
	LD 4	242.2	237.8	242.6	239.0	192.7 – 348.6
	LD 7	251.1	246.0	250.2	246.5	199.5 – 338.1
	LD 14	267.7	264.7	267.1	261.5	203.5 – 358.3
	LD 21	259.2	257.0	257.8	257.1	198.3 – 329.1
	LD 1 to 21	33.1	36.0	31.7	33.2	

Some hormones levels were examined (LH, FSH, E_2, corticosterone, progesterone and cortisol) and revealed significant changes (see Table 47).

Table 47: Hormones data

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

During gestation period, mean percentage of post-implantation loss was not significantly modified and was within the range of HCD (2.5 – 17.7 %), as it was of 5.4, 4.4, 6.4 and 6.8 %, resp. at 0, 20, 100 and 300 mg/kg bw/d. Mean duration of gestation was increased in a dose-dependent way (21.9, 22.0, 22.1 and 22.3 days, resp. at 0, 20, 100 and 300 mg/kg bw/d). 24, 25, 23 and 24 females, resp. at 0, 20, 100 and 300 mg/kg bw/d, delivered liveborn pups. 1 female at the low dose and 2 females at the highest dose had stillborn pups, moreover 1 female of the mid dose had all stillborn pups.

At necropsy, no treatment-related macroscopic findings were observed (no abnormalities were noted in 20, 20, 21 and 20 females, resp. at 0, 20, 100 and 300 mg/kg bw/d). Furthermore, final body weight and organs weight did not show any significant modifications. No histopathological examination was performed.

For F1 pups/litters:

At delivery, mean number of pups was slightly lowered in all treated groups, however the modification was not dose-related and within the range of the HCD (except for the low dose).

Table 48: Litter data

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

As observed in Table 49, an increased incidence of mortality (pups cannibalized) was noted at the highest dose between PND 1 to 4. After that, no mortality was observed. In consequence, viability index was reduced at the highest dose (92 % compared to 99 % in control group) and was outside the range of HCD (94 to 100 %). While survival index was similar in all groups (99, 100, 100 and 100 %, resp. at 0, 20, 100 and 300 mg/kg bw/d).

Table 49: Pups mortality

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

Pups body weight was examined and exhibited a significant increase at the mid dose (see Table 50). At necropsy, only 10, 15, 14 and 8 pups, resp. at 0, 20, 100 and 300 mg/kg bw/d, had macroscopic findings which were not considered as treatment-related effects.

Table 50: Pups body weight (in g)

Dose level (in mg/kg bw/d)		0	20	100	300	HCD range of study means
PND 1	M	6.8	7.1	7.4**	7.1	5.9 – 7.0
	F	6.5	6.8	7.1**	6.8	5.7 – 6.7
	M + F	6.7	6.9	7.3**	7.0	5.8 – 6.9
PND 4 (pre-culling)	M	10.5	10.8	11.6**	11.1	
	F	10.1	10.4	11.1*	10.6	
	M + F	10.4	10.6	11.3*	10.8	
PND 4 (post culling)	M	10.5	10.8	11.5**	11.1	
	F	10.2	10.4	11.2*	10.6	
	M + F	10.3	10.6	11.4**	10.8	
PND 7	M	16.6	16.8	17.8*	16.8	14.7 – 17.6
	F	16.1	16.2	17.2*	16.2	14.2 – 16.9
	M + F	16.4	16.5	17.5*	16.5	14.7 – 17.3
PND 14	M	33.0	32.8	34.3	32.6	29.3 – 35.1
	F	32.2	32.0	33.3	31.7	28.7 – 34.2

	M + F	32.6	32.4	33.8	32.1	29.2 – 34.7
PND 21	M	51.8	51.4	53.4	50.8	46.5 – 58.3
	F	50.3	49.6	51.5	49.0	45.5 – 55.7
	M + F	51.1	50.5	52.4	49.8	46.2 – 56.8

In a prenatal toxicity study (Anonymous, 1997), performed according to OECD TG 414, groups of 23-25 pregnant female Wistar rats were given by gavage test substance at a concentration of 0, 25, 100 and 400 mg/kg bw/d. Animals were exposed daily during gestational day 6 to 15.

For P adults:

During the study period, no mortality occurred. At the highest dose, 12 females out of 25 exhibited transient excessive salivation immediately after exposure. As observed in Table 51, body weight was similar in all dose groups.

Table 51: Body weight (in g)

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

Before the start of the study, 25 females per group were mated. Among these animals, 0, 1, 1 and 2 females were not pregnant, resp. at 0, 25, 100 and 400 mg/kg bw/d. During gestation, percentage of pre- and post-implantation loss were not significantly modified. Some variations were observed however change was not dose-related. At the end of the study, 25, 24, 24 and 23 dams had viable fetuses. No females had abortion or premature births and mean number of delivered fetuses was 12.8, 13.7, 12.7 and 12.7 fetuses per dam, resp. at 0, 25, 100 and 400 mg/kg bw/d.

Table 52: % of pre- and post-implantation loss

Dose level (in mg/kg bw/d)	0	25	100	400	HCD range of actual values (01/94 to 10/96)
% of pre-implantation loss	7.1	6.6	14.4	7.8	2.9 – 13.6
% of post-implantation loss	11.5	6.3	9.0	11.3	4.4 – 10.8

At the end of the study period, dams were sacrificed and necropsied. No treatment-related macroscopic findings was observed in 25, 24, 24 and 23 females, control, low, mid and high dose respectively. Organ weight (except uterus) and microscopic examination were not performed. Mean gravid uterus weight as well as net weight change were not significantly modified (see Table 53).

Table 53: Mean gravid uterus weight and net maternal body weight change (in g)

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

For F1 pups/litters:

At delivery, mean number of live fetuses, females and males, were similar in all groups. Furthermore, no significant placental as well as fetal weight were observed.

Table 54: Mean number of live pups

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

At external observation, one animal of the mid dose exhibited anophthalmia and shortened tail. At necropsy, no treatment-related soft tissue or skeletal malformations were observed.

In a prenatal developmental toxicity screening study (Anonymous, 2007), groups of 5 inseminated female rabbits were exposed daily by gavage to DMPP at a concentration of 0, 25, 100 and 400 mg/kg bw/d.

For P adults:

During the exposure period, all females exposed to 400 mg/kg bw/d were sacrificed in a moribund state at GD 14-15 (2 at GD 14 and 3 at GD 15). These animals exhibited severe clinical signs such as lateral position (4 females out of 5), apathy and poor general state (in all females), hypothermia (3 out of 5). All these clinical signs were observed at GD 14. Furthermore, no defecation was noted during GD 8 to 11 in all females exposed to 400 mg/kg bw/d. At the mid dose, no defecation was noted during GD 8 to 11 in all females, while no effects were observed in control and low dose groups.

As observed in Table 55, body weight was significantly reduced at the highest dose at GD 14.

Table 55: Body weight data (in g)

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

The percentage of pre-implantation loss was significantly increased in mid dose group, as it was of 3.1, 2.9 and 23.8** %, resp. at 0, 25 and 100 mg/kg bw/d. Furthermore, the percentage of post-implantation loss was also higher at the mid dose group, however the modification was moderate and not significant with 3.1, 2.9 and 9.7 %, resp. at 0, 25 and 100 mg/kg bw/d. At the end of the gestation period, 4, 5 and 5 dams (resp. at 0, 25 and 100 mg/kg bw/d) had viable fetuses. And the mean number of live fetuses was 7.5, 8.0 and 5.0, resp. at 0, 25 and 100 mg/kg bw/d.

At the end of the study period, dams were sacrificed and necropsied. All females exposed to 400 mg/kg bw/d had hairball in stomach and no feces in intestines, while 1 female exposed to 100 mg/kg bw/d had a missing lung lobe. Organ weight (except uterus) and microscopic examination were not performed. Gravid uterus weight was significantly decreased at the mid dose, and the net weight change showed modification which was not significant.

For F1 pups/litters:

At delivery, mean number of live fetuses was reduced at the mid dose group. As observed in Table 56, placental and fetal weights were similar in all groups.

Table 56: Mean placental an fetal body weight (in g)

Dose level (in mg/kg bw/d)	0	25	100

Placental weight	All viable fetuses	4.6	4.7	4.8
	M fetuses	4.7	4.6	5.0
	F fetuses	4.5	4.4	4.7
Fetal weight	All viable fetuses	37.5	36.7	38.6
	M fetuses	37.8	35.8	40.5
	F fetuses	36.9	37.0	37.9

At necropsy, no treatment-related external, soft tissue or skeletal malformations or variations were observed.

In a prenatal toxicity study (Anonymous, 1996), similar to OECD TG 414, groups of 10 females Wistar rats were given by gavage DMPP at a concentration of 0, 20, 80 and 320 mg/kg bw/d. Animals received the test substance daily from gestational day 6 to 15.

For P adults:

No mortality occurred during the study period, and no treatment-related clinical signs were observed. As observed in Table 57, food consumption and body weight examination did not exhibit significant change.

Table 57: Food consumption and body weight data

Dose level (in mg/kg bw/d)	0	20	80	320
Food consumption (in g/animal/day)				
GD 0 – 6	21.3	21.4	22.0	21.7
GD 6 – 15	24.8	25.2	25.3	23.5
GD 15 – 50	27.0	28.1	28.3	28.3
GD 0 – 20	24.1	24.5	24.8	24.0
Body weight (in g)				
GD 0	242.5	241.9	242.4	241.4
GD 6	267.0	268.1	267.2	265.6
GD 10	286.0	284.9	282.8	274.0
GD 15	312.3	312.0	311.0	303.4
GD 20	380.0	380.2	380.9	377.7
BWG GD 6 to 15	45.4	43.9	43.7	37.8
BWG GD 0 to 20	137.5	138.3	138.5	136.3

During gestation, the percentage of pre-implantation loss was higher at the low dose group, as it was of 8.0, 18.3, 8.7 and 8.8 %, resp. at 0, 20, 80 and 320 mg/kg bw/d. While, percentage of post-implantation loss was lowered in all treated groups compared to control. Furthermore, no abortion was noted. At the end of gestation, the number of dams with viable fetuses was of 10 (except in control group: 9 dams).

Necropsy did not reveal any treatment-related macroscopic findings. Furthermore, final body weight, plus kidneys and liver weights were examined and did not show any modification. Moreover, gravid uterus weight and net weight change were not significantly changed (see Table 58). Histopathology was not performed.

Table 58: Gravid uterus weight (in g)

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

For F1 pups/litters:

At delivery, the mean number of live fetuses was of 13.7, 12.6, 14.4 and 14.5 pups/dams, resp. at 0, 20, 80 and 320 mg/kg bw/d. Furthermore, placental and fetal weights were similar in all groups.

At necropsy, no external malformations were noted. Soft tissue observation did not reveal any malformations however variations were observed in 7, 10, 12 and 13 fetuses, resp. at 0, 20, 80 and 320 mg/kg bw/d (such as dilated renal pelvis in 7, 10, 12 and 13 fetuses and hydroureter in 0, 2, 2 and 1 fetus, resp. at 0, 20, 80 and 320 mg/kg bw/d). Incidence of skeletal malformation was not dose-related, while the incidence of skeletal variations was increased at 320 mg/kg bw/d (see Table 59).

Table 59: Fetal incidence of skeletal variations

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

In a toxicity study which examined the influence of DMPP on the phosphate metabolism of adult rats and suckling pups (Anonymous, 2017), groups of 15 female Wistar rats were exposed via diet to DMPP at a concentration of either 0 or 500 mg/kg bw/d. Animals received the test substance during 10 weeks of premating period, then for a maximum of 14 days for the mating period, plus during gestation and lactation period. In this study, a positive control (calcitriol) was also administered in an additional group.

For P adults:

During the study period, no treatment-related mortality was noted. During gestation, blood was found in the bedding of one female exposed to 500 mg/kg bw/d . Food consumption was significantly modified during the premating and gestation periods. As observed in Table 60, this parameter was higher during the first period and lower during gestation. Moreover, body weight was also significantly changed (approx. -11 % at the end of the gestation period and -9 % on LD 14, compared to the control group).

Table 60: Food consumption and body weight data

Dose level (in mg/kg bw/d)		0	500	PC
Food consumption (in g/animal/day)				
Premating and mating period		12.3	13.8*	12.1
Gestation period		19.4	14.5**	14.2**
Body weight (in g)				
Premating and mating period	D 0	106.5	106.2	106.2
	D 69	213.0	209.2	221.4
	BWG D 0 to 69	106.5	103.0	115.2
Gestation period	GD 0	217.5	216.7	221.2
	GD 7	237.3	223.3	233.2
	GD 14	263.1	238.2**	248.0
	GD 20	315.1	280.6**	296.8
	BWG GD 0 to 20	97.6	63.9**	75.5*
Lactation period	LD 1	243.2	228.8	236.6
	LD 4	260.3	231.8**	246.4
	LD 7	265.1	235.0**	256.4
	LD 14	275.2	250.7**	273.9

	BWG LD 1 to 14	32.0	21.8	37.3

Regarding female reproductive parameters, the mean number of implantation sites was reduced in the exposed group, as it was of 9 sites compared to 11 in negative control group. Among 15 mated females per group, 14 females in both negative and positive control groups were pregnant and 13 females in treated group. Fertility index was then of 93.3 % in 2 control groups and of 86.7 % in treated group. Percentage of post-implantation loss was also higher in the treated group as it was of 20 % at 500 mg/kg bw/d compared to 12 % at 0 mg/kg bw/d.

Mean duration of gestation was significantly increased in the treated group (22.8* days compared to 22.3 in negative control group). Among pregnant females, 1 of the treated group and 1 of the positive control group did not deliver. As observed in Table 61, the mean number of females with liveborn pups was reduced in the treated group, as 2 females of this group had all stillborn pups. The gestation index was then lowered in this group.

Table 61: Pregnancy data

Dose level (in mg/kg bw/d)		0	500	PC
Nb of pregnant females		14	13	14
Nb of pregnant female without delivery		0	1	1
Nb of delivery	Mean nb of pups (liveborn and stillborn)	14	12	13
	With liveborn pups (gestation index in %)	14 (100)	10 (76.5)	13 (92.9)
	With all stillborn pups	0	2	0
Nb of females with stillborn pups		1	6*	2

Necropsy did not reveal any treatment-related macroscopic abnormalities (however organ weight and microscopic examinations were not performed).

For F1 pups/litters:

At delivery, the mean number of pups per dam was of 10 in the negative control group and of 8 in the treated group. Furthermore, the mean number of liveborn pups was significantly reduced (6** in treated group compared to 10 in negative control group). As observed in Table 62, the number of pups which were found dead as well as the number of cannibalized pups were increased in the treated group even with respect to the positive control group.

Table 62: Litter data

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

As observed in Table 63, during the lactation period, pups body weight was already significantly lowered at PND 1. At PND 14, pups body weight was similar between the 2 groups. Survival index (PND 1 to 14) was of 87 % in treated group compared to 100 % of negative control group, and 96 % of the positive control. At pups necropsy, no treatment-related findings were observed.

Table 63: Pups body weight (in g)

Dose level (in mg/kg bw/d)		0	500	PC

PND 1	M + F	7.0	5.7**	6.6
	M	7.2	6.2**	6.7
	F	6.8	5.5**	6.4
PND 4	M + F	11.0	9.4**	10.2
	M	11.3	9.7*	10.4
	F	10.7	9.1*	10.0
PND 7	M + F	16.2	13.8*	15.0
	M	16.6	14.1	15.1
	F	15.8	13.5*	14.8
PND 14	M + F	29.6	26.2	27.7
	M	30.0	26.9	28.0
	F	28.7	25.7	27.3
BWG D 1 - 14	M + F	22.6	20.2	21.1

10.10.6 Comparison with the CLP criteria

Table 64: Comparison with the CLP criteria regarding developmental toxicity

Known or presumed human reproductive toxicant	Suspected human reproductive toxicant
Substances are classified in Category 1 for reproductive toxicity when they are known to have produced an adverse effect on sexual function and fertility, or on development in humans or when there is evidence from animal studies, possibly supplemented with other information, to provide a strong presumption that the substance has the capacity to interfere with reproduction in humans. The classification of a substance is further distinguished on the basis of whether the evidence for classification is primarily from human data (Category 1A) or from animal data (Category 1B). Category 1A: Known human reproductive toxicant The classification of a substance in this Category 1A is largely based on evidence from humans. Category 1B: Presumed human reproductive toxicant The classification of a substance in this Category 1B is largely based on data from animal studies. Such data shall provide clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary nonspecific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more	Substances are classified in Category 2 for reproductive toxicity when there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development, and where the evidence is not sufficiently convincing to place the substance in Category 1. If deficiencies in the study make the quality of evidence less convincing, Category 2 could be the more appropriate classification. Such effects shall have been observed in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects.

appropriate.	

Since no human studies are available for effects on development, a classification as Repr. 1A for development is not appropriate.

Several parameters regarding development were affected by the treatment:

- Mean number of pups delivered

In the two-generation reproductive toxicity study, mean number of pups of the F1 and F2 generations was lowered at the highest tested dose. The modification was significant in the F1A and F1B pups generation. Furthermore, in the pre- and post-natal toxicity study (Anonymous, 2013), lower number of pups was observed in all tested groups, even if the modification was not dose-related (see Table 65).

- Number of stillborn pups, pups which died or pups cannibalized and viability index

As observed in Table 65, all these parameters (number of stillborn pups, pups died and pups cannibalized) were significantly and severely disrupted. Due to these mortalities, viability index was reduced in the two-generation toxicity study (Anonymous, 2004), and this data was outside the range of HCD in all the examined generation. Furthermore, viability index was also examined in the pre- and post-natal toxicity study (Anonymous, 2013). In this study, viability index was outside the range of HCD for the highest dose (even if the decrease was less pronounced than in the two-generation toxicity study).

- Pups body weight

Pups body weight parameters examination exhibited divergent results. As in the two-generation reproductive toxicity study (Anonymous, 2004), pups body weight was significantly reduced at the highest dose, however change was within the range of HCD. While in the pre- and post-natal toxicity study (Anonymous, 2013), pups body weight was increased in the 2 highest doses.

➔ In conclusion, based on severe pups mortality in the first days of life, a classification as **Repr. 1B** for development is warranted.

Table 65: Summary table of developmental effects

Dose level (in mg/kg bw/d)		0	20	25	80	100	300	320	400	500	HCD
Mean nb of pups delivered											
Two-gen (Ano., 2004)	F1A	11.0	10.7	/	/	11.0	/	/	/	8.5**	9.8 – 11.7
	F1B	10.5	10.6	/	/	9.1	8.0*	/	/	/	
	F2	10.6	10.0	/	/	10.8	9.6	/	/	/	
Pre- and postnatal study (Ano., 2013)		10.5	9.1	/	/	9.4	9.3	/	/	/	9.3 – 12.8
Prenatal study (Ano., 1997) (mean nb live)		12.8	/	13.7	/	12.7	/	/	12.7	/	
Prenatal study (Ano., 2007) (mean nb live)		7.5	/	8.0	/	5.0	/	/	0 (all females sacrificed)	/	
Prenatal study (Ano., 1996) (mean nb live)		13.7	12.6	/	14.4	/	/	14.5	/	/	
Nb of females with stillborn pups (/nb of female pregnant)											
Two-gen (Ano., 2004)	F0F	5/24	2/25	/	/	2/24	/	/	/	13**/17	
	F0Y	3/23	4/23	/	/	1/23	6/23	/	/	/	
	F1F	2/21	1/24	/	/	1/25	7/20	/	/	/	
Pre- and postnatal study (Ano., 2013)		0/24	1/25	/	/	1/24	2/24	/	/	/	
Toxicity study (Ano., 2017)		1/25	/	/	/	/	/	/	/	6*/23	
Tot nb of stillborn pups											
Two-gen (Ano., 2004)	F1A	12	2	/	/	2	/	/	/	28**	
	F1B	3	4	/	/	1	10*	/	/	/	
	F2	3	1	/	/	1	15**	/	/	/	
Pre- and postnatal study (Ano., 2013)		0	1	/	/	2	3	/	/	/	0 - 7
Toxicity study (Ano., 2017)		1	/	/	/	/	/	/	/	23	
Tot nb of pups died											
Two-gen (Ano., 2004)	F1A	2	0	/	/	1	/	/	/	13**	
	F1B	0	2	/	/	0	6**	/	/	/	

	F2	2	2	/	/	3	13**	/	/	/	
Toxicity study (Ano., 2017)		0	/	/	/	/	/	/	/	8	
Tot nb of pups cannibalized											
Two-gen (Ano., 2004)	F1A	11	0	/	/	1	/	/	/	18**	
	F1B	1	1	/	/	2	14**	/	/	/	
	F2	0	3	/	/	1	6**	/	/	/	
Pre- and postnatal study (Ano., 2013)		2	2	/	/	3	16**	/	/	/	
Toxicity study (Ano., 2017)		0	/	/	/	/	/	/	/	4	
Viability index (%)											
Two-gen (Ano., 2004)	F1A	95	100	/	/	99	/	/	/	74	96 - 100
	F1B	100	99	/	/	100	90	/	/	/	
	F2	99	98	/	/	99	89	/	/	/	
Pre- and postnatal study (Ano., 2013)		99	99	/	/	99	92	/	/	/	94 - 100
Pups body weight at PND 1 (M+F) (in g)											
Two-gen (Ano., 2004)	F1A	5.9	6.2	/	/	6.2	/	/	/	5.3**	
	F1B	6.3	6.4	/	/	6.7	6.1	/	/	/	4.7 – 7.9
	F2	5.8	6.1	/	/	6.2	5.9	/	/	/	
Pre- and postnatal study (Ano., 2013)		6.7	6.9	/	/	7.3**	7.0	/	/	/	5.8 – 6.9
Toxicity study (Ano., 2017)		7.0	/	/	/	/	/	/	/	5.7**	

10.10.7 Adverse effects on or via lactation

Table 66: Summary table of animal studies on effects on or via lactation

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Two-generation reproductive toxicity study Rat (Wistar) 25/sex/group OECD TG 416 GLP	DMPP Purity: 97 % Conc.: 0, 20, 100 and 500/300 mg/kg bw/d Duration of exposure: F0 generation: 75 D before mating for M and F and until LD 21 for F. F1A pups (examined until PND 4 or 21) Second F0 generation (with same animals): 10 w premating and until weaning of F1B pups F1: 75 D of premating period and until weaning of F2 pups	Results described in Table 14	Anonymous, 2004

No human data or other data available.

10.10.8 Short summary and overall relevance of the provided information on effects on or via lactation

In a two-generation reproductive toxicity study (Anonymous, 2004), performed following OECD TG 416, groups of 25 female and 25 male Wistar rats per group were given, by diet, the test substance at a concentration of either 0, 20, 100 and 300 or 500 mg/kg bw/d.

Methods and results are described in section 10.10.2.

10.10.9 Comparison with the CLP criteria

Table 67: Comparison with the CLP criteria regarding lactation

CLP criteria
EFFECTS ON OR VIA LACTATION Effects on or via lactation are allocated to a separate single category. It is recognised that for many substances there is no information on the potential to cause adverse effects on the offspring via lactation. However, substances which are absorbed by women and have been shown to interfere with lactation, or which may be present (including metabolites) in breast milk in amounts sufficient to cause concern for the health of a breastfed child, shall be classified and labelled to indicate this property hazardous to breastfed babies. This classification can be assigned on the: (a) human evidence indicating a hazard to babies during the lactation period; and/or (b) results of one or two generation studies in animals which provide clear evidence of adverse effect

in the offspring due to transfer in the milk or adverse effect on the quality of the milk; and/or

(c) absorption, metabolism, distribution and excretion studies that indicate the likelihood that the substance is present in potentially toxic levels in breast milk.

No human information is available to demonstrate toxicity after an exposure during lactation.

The available two-generation toxicity study (Anonymous, 2004) did not demonstrate clear evidence of adverse effect in the offspring due to transfer in the milk or adverse effect on the milk quality.

10.10.10 Conclusion on classification and labelling for reproductive toxicity

Based on the available results, a classification as **Repr. 1B H360FD** is warranted.

10.11 Specific target organ toxicity-single exposure

Hazard class not assessed in this dossier.

10.12 Specific target organ toxicity-repeated exposure

Table 68: Summary table of animal studies on STOT RE

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results	Reference
Test/Palatability study RF to select doses for subchronic toxicity study Wistar rat 3/sex/dose	DMPP Oral (diet) 2 weeks Doses: 0, 5000 and 10000 ppm	No mortality occurred Bw: sign. reduced in M at the highest dose (reduced in F but not sign.) Food cons.: decreased at the highest dose in both sexes Necropsy: not performed	Anonymous, 2002
Repeated dose 28-day oral toxicity study Wistar rat 5/sex/group OECD TG 407 GLP	DMPP Purity: 99.4 % Oral (diet) 4 weeks Doses: 0, 1500, 3000 and 6500 ppm (corresp. To 0, 126.8, 215.7 and 510.4 mg/kg bw/d in M and to 0, 130.7, 255.4 and 488.7 mg/kg bw/d in F)	Clinical examination (mortality, clinical signs): no treatment-related effects observed Necropsy: macroscopic examination: no treatment-related effects Organ weight: Sign. increase in relative liver weight in M at the 2 highest doses Histopathology: higher inc and severity of degeneration/regeneration of the olfactory epithelium Increased dose-related inc and severity of diffuse atrophy of the mandibular glands LOAEL: 1500 ppm NOAEL: <1500 ppm	Anonymous, 2021

Repeated dose 28-day oral toxicity study Wistar rat 5/sex/group No OECD guideline followed GLP	DMPP Purity: 97.1 % Oral (gavage) 4 weeks + additional groups (control and high dose) for 2 weeks of recovery period Doses: 0, 20, 100 and 500 mg/kg bw/d	No mortality occurred Clinical signs: salivation, piloerection and ataxia. All findings observed after gavage and reversible BWG: sign. increased in F of the recovery group Necropsy: macroscopic: 1 female of the low dose had uterus dilatation and 1 of the mid dose had a thickening wall of the glandular stomach. Organ weight: abs and rela liver weight sign. modified at the highest dose in both sexes (not in recovery groups) + abs and rela adrenal glands weight sign. increased in M at the highest dose (but not in recovery group) Histopathology: increased incidence of hypertrophy of the adrenal cortex (in all M exposed to 500 mg/kg bw/d ; grade 2) NOAEL: 100 mg/kg bw/d	Anonymous, 1997
Subchronic oral toxicity study Wistar rat 10/sex/group OECD TG 408 GLP	DMPP Purity: 97.1 % Oral (diet) 3 months Doses: 0, 200, 1000 and 5000 ppm (corresp. to 0, 13.6, 69.2 and 353.8 mg/kg bw/d in M and to 0, 16.5, 82.1 and 400.7 mg/kg bw/d in F)	No mortality occurred No treatment-related clinical signs BWG sign. decreased at the highest dose in M (at the mid dose in F) Neurological examination (home cage observation, sensorimotor tests, FOB): no treatment-related modification Hematology and biochemical data: Hb and ALT increased and Plt decreased in M at 5000 ppm MCHC and WBC sign modified in F (ALT lowered but not sign.) Necropsy: no treatment-related macroscopic findings FBW: dose-related decrease in M Organ weight: few organs exhibited modification (adrenal, kidneys, liver, thymus) Histology: nasal cavity (level III): disarrangement observed in 8 M and 9 F at the mid dose (grade 1) and in 10 M and 10 F at the highest dose (grade 2 and 3)	Anonymous, 2003

No human data or other data available.

10.12.1 Short summary and overall relevance of the provided information on specific target organ toxicity – repeated exposure

A test/palatability study (Anonymous, 2002) was performed as a range-finding study to select doses for a next subchronic toxicity study. Groups of 3 male and 3 female Wistar rats were orally exposed to DMPP at a concentration of 0, 5000 or 10000 ppm for a period of 2 weeks.

No mortality occurred during the study period and animals did not exhibit any treatment-related clinical sign. As observed in Table 69, body weight was significantly decreased at the highest dose in males. Food consumption was also modified in this group.

Table 69: Body weight data (in g)

	Males			Females		
Dose level (in ppm)	0	5000	10000	0	5000	10000
D 0	150.0	154.5 (+3.0 %)	146.2 (-2.5 %)	119.0	117.4 (-1.3 %)	111.7 (-6.1 %)

D 7	190.2	189.9 (-0.1 %)	162.9* (-14.4 %)	137.5	132.0 (-4.0 %)	121.7 (-11.5 %)
D 14	228.4	233.6 (+2.3 %)	191.1* (-16.3 %)	151.5	145.2 (-4.1 %)	135.1 (-10.8 %)
BWG D 0-14	78.4	79.2 (+1.0 %)	44.8* (-42.8 %)	32.5	27.8 (-14.4 %)	23.4 (-27.9 %)

No information was available regarding necropsy.

In a repeated dose 28-day oral toxicity study (Anonymous, 2021), performed according to OECD TG 407, groups of 5 male and 5 female Wistar rats were given by diet the test substance at a concentration of either 0, 1500, 3000 or 6500 ppm during 4 weeks. Concentrations correspond to a mean daily test substance intake of 0, 126.8, 215.7 and 510.4 mg/kg bw/d in males and 0, 130.7, 255.4 and 488.7 mg/kg bw/d in females, resp. at 0, 1500, 3000 and 6500 ppm.

During the study period, no mortality occurred as well as no clinical signs. Furthermore, body weight did not exhibit variations (see Table 70). Neurological examination (FOB, home cage observation, sensorimotor tests and motor activity) did not reveal any treatment-related findings. Regarding haematology and biochemical examination, RBC was significantly higher in females exposed to the highest dose while in males a significant decrease of HQT was noted at this dose. A dose-related increase in males ALT was observed (see Table 71).

Table 70: Body weight data (in g)

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

Table 71: Haematology and biochemical data

	Males				Females			
Dose level (in ppm)	0	1500	3000	6500	0	1500	3000	6500
RBC (tera/L)	8.32	8.06	8.19	8.09	7.64	7.77	7.75	8.29**
Hb (mmol/L)	9.0	8.7	9.1	9.1	8.6	8.3	8.6	8.9
HT (L/L)	0.432	0.420	0.437	0.433	0.408	0.396	0.410	0.426
MCV (fL)	52.1	52.0	53.5	53.5	53.5	51.0	53.0	51.4
MCH (fmol)	1.08	1.08	1.11	1.13	1.12	1.07	1.11	1.08
MCHC (mmol/L)	20.77	20.71	20.76	21.03	20.90	21.03	20.88	20.96
Ret (%)	1.6	1.7	1.7	1.7	1.8	1.9	2.2	1.7
Plt (giga/L)	780	725	780	776	757	732	745	732
HQT (sec)	40.2	38.8	41.4	37.3*	36.1	35.4	35.3	36.1
WBC (giga/L)	7.75	6.57	6.40	6.81	4.87	5.15	4.70	5.24
ALT (µkat/L)	0.69	0.72	0.78	0.86	0.59	0.60	0.71	0.52
AST (µkat/L)	1.86	1.68	1.86	1.85	1.56	1.64	2.31	1.59
ALP (µkat/L)	2.19	2.19	2.14	2.21	1.45	1.19	1.27	1.10
GGT_C (nkat/L)	0	0	0	0	0	0	0	1

At necropsy, no treatment-related macroscopic findings were observed. Furthermore, final body weight did not show any modification. As observed in Table 72, relative liver weight was significantly and dose-related increased in males.

Table 72: Organ weight (in mg, g or %)

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

Regarding microscopic examination, 1 and 4 males of the mid and high dose groups as well as 2 females exposed to 6500 ppm had centrilobular hypertrophy in liver. Moreover, in mandibular glands, diffuse atrophy was noted. A dose-related increase was seen in both incidence and severity. Examination of the nasal cavity (level III) showed that all animals in all dose groups had degeneration/regeneration of the olfactive epithelium. Furthermore, the severity was dose-related.

Table 73: Incidence and severity of microscopic findings

		Males				Females			
Dose level (in ppm)		0	1500	3000	6500	0	1500	3000	6500
Kidneys									
Dilatation, renal pelvis	Inc	0	0	0	1	1	1	1	0
Scar(s), cortical	Inc	0	0	0	0	0	0	1	0

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

In a repeated dose 28-day oral toxicity study (Anonymous, 1997), groups of 5 male and 5 female Wistar rats were given by gavage the test substance at a concentration of either 0, 20, 100 or 500 mg/kg bw/d during a period of 28 days. Furthermore, 2 additional groups of each 5 animals/sex were exposed to the test substance at a concentration of either 0 or 500 mg/kg bw/d during 28 days. At the end of this period, these recovery groups were observed during a period of 2 weeks.

During the study period, no mortality occurred. Clinical observation revealed increased salivation, piloerection and ataxia. These effects were observed after gavage and were reversible until the next administration. As observed in Table 74, the body weight was not significantly modified (except the body weight gain (D 0 to 28) which was significantly increased at the highest dose in females of the recovery group). As observed in Table 75, main groups as well as recovery groups did not show significant haematological modification. However, ALT was dose-related increased in males and modification was also noted in the recovery group.

Table 74: Body weight data (in g)

	Males						Females					
	Main groups				Recovery groups		Main groups				Recovery groups	
Dose level (in mg/kg bw/d)	0	20	100	500	0	500	0	20	100	500	0	500
D 0	229.8	228.1	228.3	230.0	228.7	229.5	159.8	170.8	163.7	163.4	161.7	157.4

D 7	277.6	275.9	274.0	279.0	281.0	274.6	176.2	186.7	176.9	184.2	177.5	176.1
D 14	315.6	274.0	315.4	317.8	317.2	313.2	190.1	202.4	187.9	195.2	190.4	197.8
D 21	345.0	340.6	346.2	351.7	347.5	341.4	197.1	213.2	195.7	209.3	198.3	209.2
D 28	355.6	359.9	360.0	366.1	362.4	353.7	207.5	222.6	209.6	221.9	206.1	219.9
D 35	-	-	-	-	385.9	371.5	-	-	-	-	221.0	225.4
D 42	-	-	-	-	406.7	390.7	-	-	-	-	227.2	230.0
BWG D 0 to 28	125.8	131.8	131.8	136.1	133.7	124.2	47.8	51.7	45.9	58.5	44.4	62.5*
BWG D 0 to 42	-	-	-	-	178.0	161.2	-	-	-	-	65.5	72.6

Table 75: Haematological and biochemical data

		Males						Females					
		Main groups				Recovery groups		Main groups				Recovery groups	
Dose level (in mg/kg bw/d)		0	20	100	500	0	500	0	20	100	500	0	500
RBC (tera/L)	D 29	8.32	8.34	8.06	8.35	8.44	7.51	7.65	8.05	7.87	7.94	8.03	7.96
	D 43	-	-	-	-	8.58	8.19	-	-	-	-	8.08	8.05
Hb (mmol/L)	D 29	9.6	9.6	9.4	9.8	9.6	8.9	8.9	9.3	9.2	9.3	9.3	9.4
	D 43	-	-	-	-	9.5	9.7	-	-	-	-	9.4	9.5
Ht (L/L)	D 29	0.426	0.426	0.412	0.436	0.425	0.388	0.388	0.405	0.401	0.402	0.400	0.406
	D 43	-	-	-	-	0.426	0.429	-	-	-	-	0.415	0.415
MCV (fL)	D 29	51.3	51.1	51.2	52.2	50.4	51.7	50.7	50.3	50.9	50.6	49.8	51.0
	D 43	-	-	-	-	49.6	52.4	-	-	-	-	51.4	51.6
MCH (fmol)	D 29	1.16	1.16	1.16	1.18	1.14	1.18	1.17	1.16	1.17	1.18	1.15	1.18
	D 43	-	-	-	-	1.11	1.19	-	-	-	-	1.17	1.18
MCHC (mmol/L)	D 29	22.6	22.7	22.63	22.62	22.65	22.76	23.03	22.92	22.92	23.38	23.16	23.07
	D 43	-	-	-	-	22.3	22.69	-	-	-	-	22.74	22.94
Plt (giga/L)	D 29	871	869	855	919	832	829	925	862	846	893	856	950
	D 43	-	-	-	-	825	854	-	-	-	-	905	990
WBC (giga/L)	D 29	8.35	9.42	7.60	9.85	7.94	9.13	4.86	5.80	4.61	5.78	4.77	4.75
	D 43	-	-	-	-	9.42	9.07	-	-	-	-	5.50	5.12
HQT (sec)	D 29	31.5	31.4	31.0	32.1	31.9	29.9	30.1	29.5	28.9	28.4	28.2	28.1
	D 43	-	-	-	-	32.5	31.8	-	-	-	-	24.7	23.9
ALT (µkat/L)	D 29	0.78	0.9	0.9	1.18	0.8	1.09	0.66	0.72	0.79	0.77	0.68	0.73

	D 43	-	-	-	-	0.99	0.72	-	-	-	-	0.6	0.6
AST (µkat/L)	D 29	1.98	2.12	2.04	2.07	1.78	2.1	1.81	1.95	2.13	1.79	1.62	1.67
	D 43	-	-	-	-	1.61	1.76	-	-	-	-	1.46	1.96
ALP (µkat/L)	D 29	4.07	5.14	4.46	5.13	4.98	4.09	2.95	3.57	3.3	3.1	2.82	3.77
	D 43	-	-	-	-	4.35	3.65	-	-	-	-	2.55	2.98
SGGT (nkat/L)	D 29	0	1	1	1	0	3	5	8	10	14**	8	5
	D 43	-	-	-	-	10	12	-	-	-	-	15	12

At necropsy, macroscopic examination revealed only findings in 1 female of the low dose group (uterus dilatation) and in 1 female of the mid dose group (thickening of wall of the glandular stomach). Absolute and relative liver weights were significantly modified at the highest dose in both sexes of the main group. Moreover, absolute and relative adrenal glands weights were significantly higher at the highest dose in males of the main group. At the end of the recovery period, adrenal glands and liver weights were not significantly modified, however the values were higher compared to the control group (see Table 76 and Table 77). Histopathology revealed change in adrenal cortex. All males exposed to the highest dose exhibited a slight (grade 2) diffuse hypertrophy of the cortical cells. Same modification was not observed in the recovery groups. Nasal cavity histology was not performed in this study.

Table 76: Organ weight in males (in mg, g or %)

		Main groups				Recovery groups	
Dose level (in mg/kg bw/d)		0	20	100	500	0	500
FBW (g)		323.1	328.72	330.64	331.92	374.08	357.32
Adrenal glands (mg)	Abs	95.6	89.6	90.6	132.8**	89.4	105.4
	Rela	0.03	0.027	0.027	0.04**	0.024	0.03
Brain (g)	Abs	1.946	1.956	1.98	1.952	2.068	1.986
	Rela	0.605	0.596	0.601	0.589	0.553	0.557
Heart (g)	Abs	1.198	1.242	1.264	1.298	1.278	1.212
	Rela	0.372	0.378	0.383	0.392	0.341	0.339
Kidneys (g)	Abs	2.552	2.51	2.674	2.716	2.488	2.602
	Rela	0.79	0.765	0.812	0.819	0.666	0.729
Liver (g)	Abs	11.33	11.779	11.792	13.696*	12.542	12.466
	Rela	3.5	3.576	3.558	4.127**	3.35	3.478
Spleen (g)	Abs	0.666	0.682	0.668	0.764	0.768	0.684
	Rela	0.206	0.209	0.201	0.231	0.205	0.191
Thymus (mg)	Abs	443	402	456.6	533	415.6	409.6
	Rela	0.139	0.121	0.137	0.161	0.111	0.115
Epididymides (g)	Abs	0.922	0.894	0.93	0.832	1.188	0.968**
	Rela	0.287	0.273	0.282	0.251	0.318	0.272**
Testes (g)	Abs	3.372	3.318	3.138	3.028	3.4	3.334
	Rela	1.051	1.012	0.949	0.914	0.909	0.936

Table 77: Organ weight in females (in mg, g or %)

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

In a subchronic oral toxicity study (Anonymous, 2003), performed according to OECD TG 408, groups of 10 male and 10 female Wistar rats were given, by diet, test substance at a concentration of either 0, 200, 1000 or 5000 ppm (corresp. to 0, 13.6, 69.2 and 353.8 mg/kg bw/d in M and to 0, 16.5, 82.1 and 400.7 mg/kg bw/d in F). Animals were exposed daily during a period of 3 months.

During the study period, no mortality occurred and no treatment-related clinical signs were noted. As observed in Table 78, BWG was significantly decreased at the highest dose in males, while significant change was only observed at the mid dose group in females. Home cage observation, sensorimotor tests/reflexes and FOB examination did not reveal any treatment-related effects. In males, Hb was significantly higher at the highest dose while Plt was significantly lower at this dose. In females, significant changes were noted in MCHC and WBC. Clinical biochemistry examination revealed a significant increase of the ALT level in males exposed to the highest dose. In females, ALT level was lowered at the highest dose but change was not significant.

Table 78: Body weight data (in g)

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

Table 79: Haematological and biochemistry data

	Males				Females			
Dose level (in ppm)	0	200	1000	5000	0	200	1000	5000
RBC (tera/L)	8.22	8.23	8.18	8.50	7.73	7.75	7.72	7.90
Hb (mmol/L)	9.0	9.0	9.1	9.6*	8.9	8.9	8.8	9.1
Ht (L/L)	0.422	0.423	0.426	0.443	0.420	0.416	0.415	0.418
MCV (fL)	51.4	51.4	52.1	52.2	54.4	53.8	53.7	53.0
MCH (fmol)	1.10	1.10	1.12	1.13	1.15	1.15	1.15	1.16
MCHC (mmol/L)	21.40	21.38	21.48	21.62	21.19	21.47	21.29	21.76*
Plt (giga/L)	682	699	653	604*	626	659	695	689
WBC (giga/L)	5.60	5.39	5.45	5.57	2.55	3.45**	2.79	4.59**
HQT (sec)	31.4	31.6	30.8	30.9	28.3	27.8	28.1	29.9
ALT (µkat/L)	0.63	0.54	0.63	0.98*	0.73	0.66	0.74	0.52
AST (µkat/L)	1.65	1.75	2.20	2.13	3.87	2.26	2.12	1.81
ALP (µkat/L)	3.34	3.50	3.68	3.11	1.84	1.90	2.11	2.00
SGGT (nkat/L)	3	4	1	4	9	12	8	12

At necropsy, no treatment-related macroscopic findings was observed. FBW was dose-related decreased in males (approx. -3.6, -5.1 and -11 % compared to control group, resp. at 200, 1000 and 5000 ppm). As observed in Table 80, relative adrenal glands, kidneys, liver and thymus were significantly modified in males, while in females, significant modifications were observed in kidneys and liver. Histopathology revealed disarrangement in nasal cavity (level III), incidence and severity were dose-related increased as noted in Table 81. The “disarrangement” of the olfactory epithelium resulted from degenerative and regenerative processes and was located in the dorsal part of the nasal septum and the ethmoid turbinate.

Table 80: organ weight (in mg, g or %)

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

Table 81: Microscopic data

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

Table 82: Extrapolation of equivalent effective dose for toxicity studies of greater or lesser duration than 90 days

Study reference	**Effective dose (mg/kg/d)**	**Length of exposure**	**Extrapolated effective dose for 90-day exposure**	**Classification supported by the study**
Nasal cavity				
28-day study (Anonymous, 2021)	Degen./regen olf. epith. 126-130 mg/kg bw/d	28 days	Approx. 43 mg/kg bw/d	STOT RE 2
Subchronic toxicity study (Anonymous, 2003)	Disarrangement olf. epith. 1000 ppm corresp. to 69.2/82.1 mg/kg bw/d (in M/F)	90 days	69.2/82.1 mg/kg bw/d	STOT RE 2

10.12.2 Comparison with the CLP criteria

Table 83: Comparison with CLP criteria regarding STOT RE

Criteria for STOT RE 1	Criteria for STOT RE 2
"Substances that have produced significant toxicity in humans or that, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to produce significant toxicity in humans following repeated exposure. Substance are classified in category 1 for target organ toxicity (repeat exposure) on the basis of: ▪ Reliable and good quality evidence from human cases or epidemiological studies; or ▪ Observations from appropriate studies	Substances that, on the basis of evidence from studies in experimental animals can be presumed to have the potential to be harmful to human health following repeated exposure. Substances are classified in category 2 for target toxicity (repeat exposure) on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentrations." "Classification in category 2 is applicable, when significant toxic effects observed in a 90-day

in experimental animals in which significant and/or severe toxic effects, of relevance to human health, were produced at generally low exposure concentrations." "Classification in category 1 is applicable, when significant toxic effects observed in a 90-day repeated dose study conducted in experimental animals are seen to occur at or below the guidance value (C) as indicated in table 3.9.2" Route of exposure / Units / Guidance value Oral (rat) / mg/kg bw/d / C≤10	repeated dose study conducted in experimental animals are seen to occur within the guidance value range as indicated in table 3.9.3" Route of exposure / Units / Guidance value range Oral (rat) / mg/kg bw/d / 10 < C ≤ 100

4 repeated dose toxicity studies were available and demonstrated toxicity in some organs/systems:

- Nasal cavity:

Among the 4 repeated dose toxicity studies, nasal cavity were not examined in the test/palatability study (Anonymous, 2002) as well as in the second repeated dose toxicity study (Anonymous, 1997). In the 2 other available studies, nasal cavity was affected.

In the repeated dose 28-day oral toxicity study (Anonymous, 2021), histology of nasal cavity level III revealed an increased incidence of degeneration/regeneration of the olfactive epithelium. All animals (males and females) of treated groups were affected. Furthermore, the increase in the severity was dose-related. As animals were exposed during 28 days, range to classify a substance as STOT RE in category 2 was of 30 to 300 mg/kg bw/d. Low and mid dose groups, which were within the range of category 2, demonstrated degeneration/regeneration of olfactive epithelium in all animals and the effect was of grade 1 to 3.

Moreover, in the subchronic oral toxicity study (Anonymous, 2003), nasal cavity was also affected as disarrangement was noted at the 2 highest doses (1000 and 5000 ppm). At the mid dose (1000 ppm), which correspond approximately to 69.2 and 82.1 mg/kg bw/d resp. in males and females, 8 males and 9 females out of 10 per sexe exhibited disarrangement of the olfactive epithelium. This dose level was within the range to classify in category 2.

Table 84: Summary table of nasal cavity's effects

		Males							Females						
Dose level (in mg/kg bw/d)		0	13	69	126	215	353	510	0	16	82	130	255	400	488
28-day study (Anonymous, 2021)															
Degen/ regen olf. epith.	Inc	0	/	/	5	5	/	5	0	/	/	5	5	/	5
	Grade 1				4							3	2		
	Grade 2				1	2						2	1		
	Grade 3					3		3					2		2
	Grade 4							2							3

90-day study (Anonymous, 2003)															
Disarrangement of the olf epith	Inc	0	0	8	/	/	10	/	0	0	9	/	/	10	/
	Grade 1			8							9				
	Grade 2						7							3	
	Grade 3						3							7	

In grey: dose in the range to classify in category 2

Two repeated dose toxicity studies demonstrated that the test substance affects the epithelium of the nasal cavity. Almost every exposed animal exhibited lesion, and in the 28-day repeated dose of exposure, the epithelium was severely disrupted in 3 males out of 5 and in 2 females out of 5. In the two studies, the incidence was dose-related as well as the severity.

As mentioned in the CLP Guidance, section 3.9.1 Definition and General considerations for STOT RE, *"Specific target organ toxicity (repeated exposure) means specific, target organ toxicity arising from a repeated exposure to a substance or mixture.* ***All significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed are included****."*.

Based on the available results, a classification as **STOT RE Cat. 2 for the nasal cavity** is warranted.

- Liver:

Liver was examined in 3 different repeated dose toxicity studies.

In the 28-day repeated dose oral toxicity study (Anonymous, 2021), ALT increased in males. Change was dose-related but not significant. Modification was not observed in females. At necropsy, relative liver weight was significantly increased in males at the 2 highest dose and the change was dose-related. As for the enzyme, modification was more moderate in females, which exhibited only a non-significant increase. Histology revealed an increased incidence of centrilobular hypertrophy at the 2 highest doses. Based on the exposure period and the CLP Regulation, the range to classify in category 2 was of 30 and 300 mg/kg bw/d. In this study, the low and the mid dose groups (approx. 126/130 and 215/255 mg/kg bw/d in M/F) were within the range to classify in category 2. At this dose, liver weight was not significantly affected and the incidence of centrolobular hypertrophy was of 1 male out of 5.

In the another 28-day oral repeated dose toxicity study (Anonymous, 1997), the dose-related increase in ALT level was not significant. At necropsy, liver weight was examined and was significantly modified at the highest dose which was outside the range of STOT RE Cat 2.

In the 90-day oral repeated dose toxicity study (Anonymous, 2003), ALT was significantly increased at the highest dose in males, however modification was not dose-related and the highest dose was outside the range to classify in category 2. Furthermore, at necropsy, liver weight was significantly changed at the highest dose and 5 males and 5 females exhibited minimal centrolobular hypertrophy. Histology was not examined at the low and mid dose groups.

As observed in Table 85, DS is of the opinion that liver adverse effects observed in the range to classify in category 2 is not enough to warrant a classification for liver.

Table 85: Summary table of liver's effects

		Males										Females									
Dose level (in mg/kg bw/d)		0	13	20	69	100	126	215	353	500	510	0	16	20	82	100	130	255	400	488	500
28-day study (Anonymous, 2021)																					
ALT (µkat/L)		0.69	/	/	/	/	0.72	0.78	/	/	0.86	0.59	/	/	/	/	0.60	0.71	/	0.52	/
AST (µkat/L)		1.86	/	/	/	/	1.68	1.86	/	/	1.85	1.56	/	/	/	/	1.64	2.31	/	1.59	/
ALP (µkat/L)		2.19	/	/	/	/	2.19	2.14	/	/	2.21	1.45	/	/	/	/	1.19	1.27	/	1.10	/
Liver weight (g or %)	Abs	6.986	/	/	/	/	7.25	6.94	/	/	7.85	4.74	/	/	/	/	4.64	5.12	/	4.99	/
	Rela	2.57	/	/	/	/	2.67	2.71*	/	/	2.91**	2.71	/	/	/	/	2.70	2.88	/	2.86	/
Hypertrophy, centrilobular	Inc	0	/	/	/	/	0	1	/	/	4	0	/	/	/	/	0	0	/	2	/
	Grade 1							1			4									1	
	Grade 2																			1	
28-day study (Anonymous, 1997)																					
ALT (µkat/L)		0.78	/	0.9	/	0.9	/	/	/	1.18	/	0.66	/	0.72	/	0.79	/	/	/	/	0.77
AST (µkat/L)		1.98	/	2.12	/	2.04	/	/	/	2.07	/	1.81	/	1.95	/	2.13	/	/	/	/	1.79
ALP (µkat/L)		4.07	/	5.14	/	4.46	/	/	/	5.13	/	2.95	/	3.57	/	3.3	/	/	/	/	3.1
Liver weight (g or %)	Abs	11.3	/	11.78	/	11.8	/	/	/	13.7*	/	5.82	/	6.3	/	6.4	/	/	/	/	7.6*
	Rela	3.5	/	3.6	/	3.6	/	/	/	4.13**	/	3.04	/	3.1	/	3.4	/	/	/	/	3.73**
90-day study (Anonymous, 2003)																					
ALT (µkat/L)		0.63	0.54	/	0.63	/	/	/	0.98*	/	/	0.73	0.66	/	0.74	/	/	/	0.52	/	/
AST (µkat/L)		1.65	1.75	/	2.20	/	/	/	2.13	/	/	3.87	2.26	/	2.12	/	/	/	1.81	/	/
ALP (µkat/L)		3.34	3.50	/	3.68	/	/	/	3.11	/	/	1.84	1.90	/	2.11	/	/	/	2.00	/	/
Liver (g)	Abs	8.66	8.24	/	8.12	/	/	/	8.52	/	/	5.03	4.84	/	5.08	/	/	/	5.63*	/	/
	Rela	2.38	2.35	/	2.3	/	/	/	2.64**	/	/	2.49	2.43	/	2.71	/	/	/	2.80**	/	/
Minimal centrolobular hypertrophy	Inc	0	NE	/	NE	/	/	/	5	/	/	0	NE	/	NE	/	/	/	5	/	/

In grey: dose in the range to classify in category 2

10.12.3 Conclusion on classification and labelling for STOT RE

Based on the available results, a classification as **STOT RE Cat. 2 H373 (nasal cavity)** is warranted.

10.13 Aspiration hazard

Hazard class not assessed in this dossier.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

Not evaluated in this CLH dossier.

12 EVALUATION OF ADDITIONAL HAZARDS

Not evaluated in this CLH dossier.

13 ADDITIONAL LABELLING

NA

14 REFERENCES

Full study reports

Registration dossier

15 ANNEXES

Annex I to the CLH report

16 ABBREVIATIONS

*: $p<0.05$

**: $p<0.01$

Abs: absolute

ALD: aldosterone

ALP: alkaline phosphatase

ALT: alanine aminotransferase

Ano.: anonymous

Approx.: approximately
AST: aspartate aminotransferase
ATE: acute toxicity estimate
BW: body weight
BWG: body weight gain
Cat: category
CC: corticosterone
Chol: cholesterol
Conc: concentration
Cons.: consumption
Corresp.: corresponding
Degen.: degeneration
DPC: day post-coitum
E2: estradiol
Epith: epithelium
Exp: experiment
F: female
FBW: final body weight
FOB: functional observation battery
FSH: follicle stimulating hormone
GD: gestational day
GGT_C: serum-y-glutamyltransferase
GLDH: glutamate dehydrogenase
GLP : good laboratory practice
Hb: hemoglobin
HCD: historical control data
HQT: prothrombine time (hepato Quick's test)
Ht: hematocrit
Inc: incidence
Infiltr: infiltration
Inflamm: inflammation
Irrit: irritation
LC50: lethal concentration 50 %
LD: lactation day
LD50: lethal dose 50 %
LH: luteinizing hormone
LOAEL: low observed adverse effect level

M: male

MCH: mean corpuscular hemoglobin

MCHC: mean corpuscular hemoglobin concentration

MCV: mean corpuscular volume

Min: minimum

Nb: number

NE: not examined

NOAEL: no observed adverse effect level

NT: not tested

Olf.: olfactive

PC: positive control

PI: post-implantation

Plt: platelet

PND: post-natal day

RBC: red blood cell

Regen.: regeneration

Rela: relative

Repr: reprotoxic

Resp: respectively

Ret: reticulocyte

RF: range-finding

SGGT: gamma-glutamyl transferase

Sign: significant(-ly)

St. Dev.: standard deviation

STOT RE: specific target organ toxicity – repeated exposure

STOT SE: specific target organ toxicity – single exposure

T: testosterone

TBD: to be defined

TG: test guideline

Tot: total

Tot prot: total protein

Tox: toxicity

WBC: white blood cell