

CLH report

Proposal for Harmonised Classification and Labelling

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

International Chemical Identification: 4,4'-sulphonyldiphenol; bisphenol S

EC Number: 201-250-5

CAS Number: 80-09-1

Index Number: NA

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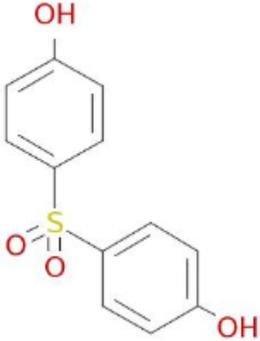
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1 IDENTITY OF THE SUBSTANCE

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)	4-(4-hydroxybenzenesulfonyl)phenol
Other names (usual name, trade name, abbreviation)	<p>Bisphenol S</p> <p>1,1'-Sulfonylbis[4-hydroxybenzene]</p> <p>4,4'-Bisphenol S</p> <p>4,4'-Dihydroxydiphenyl sulfone</p> <p>4,4'-Sulfonylbisphenol</p> <p>4,4'-Sulfonyldiphenol</p> <p>4-Hydroxyphenyl sulfone</p> <p>Bis(4-hydroxyphenyl) sulfone</p> <p>Bis(hydroxyphenyl)sulfone</p> <p>BIS(HYDROXYPHENYL)SULPHONE</p> <p>Bis(p-hydroxyphenyl) sulfone</p> <p>BPS 1</p> <p>Dihydroxydiphenyl sulfone</p> <p>DIHYDROXYDIPHENYLSULPHONE</p> <p>Diphone C</p> <p>p,p'-Dihydroxydiphenyl sulfone</p> <p>Phenol, 4,4'-sulfonylbis- (9CI)</p> <p>Phenol, 4,4'-sulfonyldi- (6CI, 8CI)</p> <p>Phenol, sulfonylbis-</p> <p>Phenol, sulfonyldi-</p> <p>PHENOL, SULPHONYLBIS</p> <p>PHENOL, SULPHONYLDI</p> <p>Sulfonyldiphenol-</p> <p>SULPHONYLDIPHENOL</p>
EC number (if available and appropriate)	201-250-5
EC name (if available and appropriate)	4,4'-sulphonyldiphenol
CAS number (if available)	80-09-1
Molecular formula	C ₁₂ H ₁₀ O ₄ S

Structural formula	
SMILES notation (if available)	
Molecular weight or molecular weight range	250.27
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)	≥ 99.7 %

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 Annex VI (CLP)	CLH in Table 3.1	Current self-classification and labelling (CLP)
4,4'-sulphonyldiphenol EC n° : 201-250-5	≥ 99.7 -100.0 % (W/W)	NA		Self classification in the public REACH registration dossiers: - Repr. 2, H361 - Not classified

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 Annex VI (CLP)	CLH in Table 3.1	Current self-classification and labelling (CLP)	The impurity contributes to the classification and labelling
See confidential Annex					The impurities do not contribute to the classification

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 3.1 (CLP)	Current self-classification and labelling (CLP)	The additive contributes to the classification and labelling
None					

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 5:

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	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 submitters proposal	TBD	4,4'-sulphonyldiphenol; bisphenol S	201-250-5	80-09-1	Repr. 1B	H360FD	GHS08 Dgr	H360FD			
Resulting Annex VI entry if agreed by RAC and COM	TBD	4,4'-sulphonyldiphenol; bisphenol S	201-250-5	80-09-1	Repr. 1B	H360FD	GHS08 Dgr	H360FD			

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	hazard class not assessed in this dossier	No
Acute toxicity via dermal route	hazard class not assessed in this dossier	No
Acute toxicity via inhalation route	hazard class not assessed in this dossier	No
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	hazard class not assessed in this dossier	No
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

4,4'-sulphonyldiphenol (BPS) is a chemical substance which is registered under the REACH Regulation (1907/2006/EC). The substance is not listed in annex VI of CLP and classification and labelling was not previously discussed by the TC C&L.

The C&L inventory contains several different self classifications for this substance (C&L Inventory, 9/7/2019) :

- Repr. 2, H361 (fertility)
- Not classified
- Skin Irrit. 2, H315
- Eye Irrit. 2, H319
- STOT SE 3, H335
- Aquatic chronic 3, H412

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

No justification is needed. The substance is self classified as a reprotoxicant.

Currently 4,4'- sulphonyldiphenol is self-classified as Repr. 2 in 2 out of the 3 public REACH registration dossiers. However based on the available data classification as Repr. 1B H360FD is warranted.

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

[B.] Justification that action is needed at Community level is required.

Reason for a need for action at Community level:

Disagreement by DS with current self-classification

5 IDENTIFIED USES

The substance is used in articles, by professional workers, in formulation or re-packaging at industrial sites and in manufacturing.

No public registered data are available indicating whether or in which chemical products the substance might be used.

However 4,4'- sulphonyldiphenol is reported in the literature (Molina-Molina *et al.*, 2013) to be used in high temperature resistant thermoplastic polymers :

- In BPS-based epoxy resins and
- as monomer in the production of cyclic carbonates and sulfonated poly(ether ketone ether sulfone)

Some other uses are reported in the same article:

- chemical additive in pesticides, dyestuffs, colour-fast agents, leather tanning agents, dye dispersants and fiber improvers.
- as a developer in dyes for thermal paper (as alternative to Bisphenol A or BPA).

Finally, 4,4'-sulphonyldiphenol has been detected in canned food and in paper products and currency bills.

6 DATA SOURCES

Registration dossier (last modification : 20-Mar-2019 ; consultation by the DS : 24-June-2019; <https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/14986/1>)

C&L inventory : consulted by the DS : 9/7/2019

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	A fine white odourless powder	- Anonymous 1, 2012 - Anonymous 2, 2009 -GESTIS Substance database, 2008	value used for Chemical Safety Assessment (CSA) : solid at 20° C and 101.3 kPa
Melting/freezing point	245-248° C	Beilstein, 2007 BGIA Gestis Stoffdatenbank, 2008	Beilstein covers a melting point of 245 - 248° C as a range of 8 independent entries. GESTIS gives 242 -247° C as value for the melting point. The range of values cited in Beilstein was taken as key value. Reliability 2
Boiling point	Not applicable	Study report, 2010 Anonymous 3	OECD TG 103, dynamic method decomposition at 315° C The boiling point of the test item could not be determined, because at a temperature of 315° C a continuously increasing pressure was observed. This is presumably caused by a limited stability and a thermal change of the test item. Reliability 1
Relative density	-1.37 g/cm ³ at 15° C -1.37 g/cm ³ at 15° C -1.4 g/cm ³ at 15° C	- Annaheim, 2007 - Yaws, Carl L., 2009 - Beilstein, 2007	Measured Reliability 2
Vapour pressure	Negligible 6.29E-10 hPa at 25° C	Neely WB & Howard PH, 1995	The melting point of the substance is between 200°C and 300° C The calculated value of vapour pressure at 25° C (MPBPWIN v1.42) is quite low as expected
Surface tension	Not applicable		Based on chemical structure, no surface activity is predicted.
Water solubility	- 1.1 g/L at 20° C	- BGIA Gestis Stoffdatenbank,	- Measured (Key study, Reliability 2), Value used for CSA: 1.1 g/L at 20° C

Property	Value	Reference	Comment (e.g. measured or estimated)
	- 505 mg/L at 25° C - 1774 mg/L at 25° C - ca. 1.1 g/L at 20° C	2008 - Meylan WM <i>et al.</i> , 1996 - BASF AG, 2007 - Clairant, 2004	- Calculated (Reliability 2) - Calculated (Reliability 2) - Measured (Reliability 4)
Partition coefficient n-octanol/water	-log Pow = 1.2 at 23° C, pH 6.2 -log Pow = 1.65 at 25° C -log Pow = 1.65 at 25° C -log Pow = 1.65 at 25° C	- Study report, 2010 Anonymous 4 - Peer review database, 2007 Anonymous 5 - Meylan WM, & Howard PH., 1995 - Peer review database, 2009 Anonymous 6	- OECD TG 117 Measured (key study, Reliability 2) - EPIWin calculation KOWWIN v1.67 (Reliability 2) - Model calculation (Reliability 2) - Calculation (Reliability 2)
Flash point	Not applicable		The substance is a solid.
Flammability	- The substance is not a highly flammable solid. - No selfheating up to 350° C. - Combustible solid	- Study report, 2009 Anonymous 7 - 2006, anonymous 8 - BGIA Gestis Stoffdatenbank, 2008	- EU Method A.10 (Key study, reliability 2) - according to VDI 2263 (Reliability 2) - measured (Reliability 2) Value used for CSA: Non flammable solid. Based on chemical structure pyrophoric properties and flammability in contact with water are not to be expected. The substance or mixture does not need to be classified as self-reactive as the heat of decomposition is less than 300 J/g. The substance or mixture does not need to be classified as self-heating as the onset temperature is greater than 220 °C in the Grewer Oven test (screening test). The substance or mixture does not need to be classified as an organic peroxide as by definition based on their chemical structure the substance is no organic peroxide.
Explosive properties	Non explosive		Value used for CSA: non explosive There are no chemical groups associated with explosive properties present in the molecule
Self-ignition temperature	- No Self ignition up to 350° C - ≥ 400 °C at	- study report, 2006 Anonymous 9 - Clairant, 2004	- EU Method A.16 (Reliability 2) - According to DIN 51 794 (Reliability 4) The substance is a solid and self-heating of the substance up to 400° C is excluded.

Property	Value	Reference	Comment (e.g. measured or estimated)
	1013 hPa		
Oxidising properties	No oxidising properties	Study report, 2010 Anonymous 10	EU Method A.17 (Reliability 1) Value used for CSA: Oxidising: no The test substance is not considered an oxidising substance because the maximum burning rate of the mixtures tested is lower than the maximum burning rate of the reference mixture
Granulometry	- Particles <100 µm approximate 55 %, - Particles <10 µm approximate 1.8 %, - Particles <4 µm approximate 0.4 %	Study report, 2009 Anonymous 11	OECD TG 110
Stability in organic solvents and identity of relevant degradation products	Not applicable		The stability of the substance is not considered as critical.
Dissociation constant	- pKa=8 at 20° C - pKa=7.93 at 25°C - pKa=8.14 at 25°C	- Study report, 2009 Anonymous 2 - BASF SE, 2008	- OECD TG 112 (Key study, reliability 2) - SPARC calculation (Reliability 2)
Viscosity	Not applicable		Substance is a solid at 20° C and atm. pressure

8 EVALUATION OF PHYSICAL HAZARDS

Not evaluated in this dossier

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

Not evaluated in this dossier

10 EVALUATION OF HEALTH HAZARDS

10.1 Acute toxicity - oral route

Not evaluated in this dossier

10.2 Acute toxicity - dermal route

Not evaluated in this dossier

10.3 Acute toxicity - inhalation route

Not evaluated in this dossier

10.4 Skin corrosion/irritation

Not evaluated in this dossier

10.5 Serious eye damage/eye irritation

Not evaluated in this dossier

10.6 Respiratory sensitisation

Not evaluated in this dossier

10.7 Skin sensitisation

Not evaluated in this dossier

10.8 Germ cell mutagenicity

Not evaluated in this dossier

10.9 Carcinogenicity

Not evaluated in this dossier

10.10 Reproductive toxicity

10.10.1 Adverse effects on sexual function and fertility

Table 8: Summary table of animal studies on adverse effects on sexual function and fertility

Method, species, no/group	guideline, strain, sex, levels of exposure	Test substance, dose duration of exposure	Results	Reference
Reproductive toxicity test Rats / Spargue-Dawley (SD) 12/sex/group Gavage Following OECD TG 421 GLP	4,4'-sulphonyldiphenol Vehicle : 0.5 % aqueous sodium CMC solution with 0.1 % Tween 80 Doses : 0, 10, 60 and 300 mg/kg bw/d Exposure : a total (tot.) of 45 D for males (including 14 D of premating period, through mating to the day before necropsy) and a total of 40 to 46 D for females (from premating, mating, gestation until lactation day (LD) 3) (females without delivery were exposed until D 25 after confirmation of copulation)	4,4'-sulphonyldiphenol	<p><u>Parental generation :</u></p> <p>Clinical signs : excessive salivation at 300 mg/kg bw/d</p> <p>Body weight (bw) : reduced at the highest dose in both sexes (see table 9)</p> <p>Gross necropsy findings : distension of cecum observed in 1 male (♂) and 1 female (♀) in the mid dose level and in all ♂ and 4 ♀ at the highest dose level</p> <p>Organ weight : in ♂ : sign. increase of relative (rel.) pituitary and rel. liver weights and sign. decrease of seminal vesicle weight (see table 12)</p> <p>In ♀ : no sign. changes at the highest dose observed</p> <p>Histopathology : cecum : sign. increased incidence of hyperplasia of the mucosal epithelium (epith.) (in 11 ♂) and sign. higher incidence of single cell necrosis (in 5 ♂) at the highest dose</p> <p>Liver : centrilobular hypertrophy of hepatocytes observed in 5 ♂ at 300 mg/kg bw/d</p> <p>Reproductive data : copulation index, parturition index, delivery index, number (nb) of corpora lutea, gestation period : no effects</p> <p>The mean duration of oestrus cycle was sign. higher at the highest dose (5.57**d vs 4.08d in control group) and 5 ♀ exposed to 300 mg/kg bw/d exhibited a longer dioestrus period (vs 0 ♀ in control).</p> <p>Decreased mean nb of implantation sites at 300 mg/kg bw/d (10.7 vs 15.9 in control group) and sign. lower implantation index at 300 mg/kg bw/d (64.89** % vs 95.80 % in control group)</p> <p>Severe decrease of fertility index : 58.3 % at the highest dose vs 91.7 % in control group</p> <p><u>Offspring :</u></p> <p>Decreased mean nb of offspring at birth at 300 mg/kg bw/d (9.1 at 300 mg/kg bw/d vs 14.3 in control group)</p>	Anonymous 12, 2000

Method, species, no/group, guideline, strain, sex,	Test substance, dose levels, duration of exposure	Results	Reference
		No abnormalities in external appearance and clinical signs nor bw, body weight gain (bwg), viability index, ano-genital distance (AGD)	
<p>Extended-one-generation reproductive toxicity study (EOGRTS) with F2, developmental neurotoxicity (DNT) (cohorts 2A and 2B) and developmental immunotoxicity (DIT) (cohort 3) Rats / SD</p> <p>F0 generation : 24/sex/dose</p> <p>F1 generation : 20/sex/dose for cohort 1A, 24/sex/dose for cohort 1B, 10/sex/dose for cohorts 2A, 2B and 3</p> <p>Gavage</p> <p>Following OECD TG 443 GLP</p>	<p>4,4'-sulphonyldiphenol</p> <p>Vehicle : 0.5 % CMC</p> <p>Doses : 0, 20, 60 and 180 mg/kg bw/d</p> <p>Duration of exposure : Minimum 10 w after the beginning of exposure, males and females from the same dose group were mated. Shortly before weaning of the F1 pups, the F0 males were sacrificed whereas, the F0 females were sacrificed after weaning of the F1 pups. Before weaning of the F1 pups on PND 21, 74 animals/sex/group were randomly selected and, after weaning, placed into cohorts.</p>	<p><u>Parental generation :</u></p> <p>Bw : sign. higher only in ♀ during the in-life period (D 7 and 14 in the mid dose)</p> <p>♂ reproductive data : sign. reduction in % of motile sperm in all tested dose group (88, 84*, 85* and 86* %, respectively at 0, 20, 60 and 180 mg/kg bw/d)</p> <p>♀ reproductive data : mean duration of oestrus cycle : sign. increase at 180 mg/kg bw/d (4.1* d vs 3.9d in control)</p> <p>Mean nb of implantation site : reduced at the highest dose (14.3 vs 15.3 in control)</p> <p>Mean nb of post-implantation loss sign. affected (1.5** vs 0.5 in control)</p> <p>Necropsy : enlarged cecum and changes in kidneys observed in ♂ at 180 mg/kg bw/d</p> <p><u>F1 pups :</u></p> <p>Sign. lower tot. nb. of liveborn pups (285* at 180 mg/kg bw/d vs 340 in control) and sign. higher nb of stillborn pups (8* at 180 mg/kg bw/d vs 2 in control)</p> <p><u>Cohort 1A :</u></p> <p>Final body weight (FBW) : slightly reduced at 180 mg/kg bw/d in ♂</p> <p>BW : in ♀, body weight was sign. higher at D14 and D28 in the mid and high dose groups</p> <p>Necropsy : adrenal glands, kidneys, liver, spleen, thymus and prostate showed a significant deviation in absolute (abs.) or rel. value</p> <p>An atrophy of the mammary gland was noted in ♂ of the highest dose</p> <p><u>Cohort 1B :</u></p> <p>higher mean duration of oestrus cycle at 180 mg/kg bw/d (4.5 d vs 3.9 d in control)</p> <p>Lower mean nb of implantation sites and sign. higher incidence of post-implantation loss at 180 mg/kg bw/d</p> <p>Necropsy : FBW slightly reduced in ♂ at the highest dose and a few organ weights modified</p> <p><u>Cohort 2A :</u></p> <p>Auditory startle response, home cage</p>	<p>Anonymous 13, 2019</p>

Method, species, no/group	guideline, strain, sex, Test substance, levels duration of exposure	dose of Results	Reference
		<p>observations, open field observations, sensorimotor tests/reflexes, motor activity measurements and learning and memory tests : unaffected</p> <p><u>Cohor 2B :</u></p> <p>Necropsy examination : no effects observed</p> <p><u>Cohort 3 :</u></p> <p>Clinical and bw examination : unaffected</p> <p>Necropsy examination : sign lower rel. thymus weight at 180 mg/kg bw/d</p> <p>T-cell dependent antibody response : slight change in the low and mid dose groups in ♀</p> <p><u>F2 pups :</u></p> <p>Decrease tot. nb of pups delivered at the highest dose</p>	
<p>Range finding study preceding the EOGRTS, Similar to a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test</p> <p>Rats / SD</p> <p>10/sex/dose</p> <p>Gavage</p> <p>Similar to OECD TG 422</p> <p>GLP</p>	<p>4,4'-sulphonyldiphenol</p> <p>Vehicle : CMC</p> <p>Doses : 0, 30, 100 and 300 mg/kg bw/d</p> <p>Duration of exposure : 10 w for males and continued through pre-mating, gestation, and lactation periods for females</p>	<p><u>F0 generation :</u></p> <p>Mortality : no premature death</p> <p>Clinical signs : excessive salivation observed at the highest dose</p> <p>Bw : lowered at the highest dose (-7 % in ♂ and -6 % in ♀ compared to the control group)</p> <p>Haematology and clinical biochemistry : no effects (no further information available)</p> <p>Gross pathological findings : increased incidence of cecum dilatation, enlarged and discoloration of kidneys and enlarged liver in ♂ exposed to 300 mg/kg bw/d</p> <p>Organ weight : sign. higher rel. kidneys weight in ♂ (+11.5 and +35 % respectively at 100 and 300 mg/kg bw/d) and sign higher rel. liver weight in ♂ at the highest dose (+11 %). In ♀, uterus weight modified at 300 mg/kg bw/d</p> <p>Histopathology : changes observed in liver in both sexes. Furthermore, mammary gland and cecum also affected in ♂</p> <p><u>Reproductive data :</u></p> <p>Oestrus cycle : prolonged at the highest dose (5.16** vs 4.02 d in control group)</p> <p>Sign. lower mean nb. of implantation sites at 300 mg/kg bw/d (10.4** vs 15.8 in control group)</p> <p>% of post-implantation loss : sign. higher at 300 mg/kg bw/d (34.6* vs 3.6 % in control group)</p>	<p>Anonymous 14, 2017</p>

Method, species, no/group	guideline, strain, sex,	Test substance, dose levels duration of exposure	Results	Reference
			<p>F1 :</p> <p>Mean nb of pups delivered sign decreased at the highest dose (10.8** vs 15.2)</p> <p>Pups bw sign. higher in ♂ of the low dose at PND 21 (+6.6 % compared to the control group) (no further information available)</p> <p>Gross pathological findings : no effects observed (no further information available)</p>	
<p>Range finding study preceding the EOGRTS, similar to a 28 D repeated dose toxicity study</p> <p>Rat / SD</p> <p>5/sex/dose</p> <p>Gavage</p> <p>No guideline followed</p> <p>GLP : no</p>		<p>4,4'-sulphonyldiphenol</p> <p>Vehicle : CMC</p> <p>Dose : 0, 100, 300 and 600 mg/kg bw/d</p> <p>Duration of exposure : 28 D</p>	<p>Clinical signs : excessive salivation</p> <p>BWG : sign. lower at the highest dose in ♂ (no further information available)</p> <p>FBW : lower at the mid and high dose levels (-9 and -12 % respectively at 300 and 600 mg/kg bw/d)</p> <p>Gross necropsy findings : enlarged kidneys observed in 4 ♂ exposed to 600 mg/kg bw/d and in 3 ♂ exposed to 300 mg/bw/d. Moreover, cecum dilatation was noted in 2 ♂ of the highest dose.</p> <p>Organ weight : a few changes observed in kidneys, adrenals, liver, prostate and sem. ves.</p> <p>Histopathology : a few changes observed in kidneys, adrenal glands, liver, cecum and mammary gland.</p>	<p>Anonymous 15, 2017</p>
<p>28-days repeated dose toxicity study including 2-weeks observation of reversibility</p> <p>Rat / SD</p> <p>6/sex/group (for main group) + 6/sex/group (for recovery group)</p> <p>Gavage</p> <p>Similar to OECD TG 407</p> <p>GLP</p>		<p>4,4'-sulphonyldiphenol</p> <p>Vehicle : 0.5 % aqueous solution of methylcellulose</p> <p>Conc. : 0, 40, 200 and 1000 mg/kg bw/d for main groups</p> <p>0, 200 and 1000 mg/kg bw/d for recovery groups</p> <p>Duration of exposure : 28 d, daily</p> <p>Observation period : 2 w for recovery groups</p>	<p>Mortality : 2 ♂ exposed to the highest dose (dilatation of cecum and signs of intestine haemorrhage at necropsy)</p> <p>Clinical signs : 1000 mg/kg bw/d : abdominal distension in 1 ♀ after 15 days and in 5 ♀ after 28 days (this effect disappeared during the recovery period)</p> <p>BW : lower value at 1000 mg/kg bw/d during the dosing period (sign in ♂). Recovered at the end of the recovery period</p> <p>BWG : sign. lower in both sexes for the exposure period and sign. reduce in ♂ for the recovery period</p> <p><u>Animals necropsied at the end of dosing period :</u></p> <p>Gross pathology findings : 1000 mg/kg bw/d : dilatation of cecum in all animals</p> <p>Organ weight : few modification (see table 29)</p> <p>Histopathological findings observed in cecum (hyperplasia of mucosa, single cell necrosis of mucosal epithelium), liver (hypertrophy centrilobular), adrenals (hypertrophy of zona fasciculate), femur (increase spongy bone) and</p>	<p>Anonymous 16, 1999</p>

Method, species, no/group	guideline, strain, sex,	Test substance, dose levels duration of exposure	Results	Reference
			<p>thymus (atrophy)</p> <p><u>Animals necropsied at the end of recovery period :</u></p> <p>Gross pathology findings : dark red spots in the glandular stomach in 2 ♀ of the mid dose and in 2 ♀ of the high dose.</p> <p>Organ weight : few modifications</p> <p>Histopathological findings observed in cecum (hyperplasia of mucosa and single cell necrosis of mucosal epithelium), liver (microgranuloma) and femur (increase spongy bone)</p>	
<p>90-day repeated dose toxicity study</p> <p>Rat / Wistar / males + females</p> <p>10/sex/dose</p> <p>Gavage</p> <p>Following OECD TG 408</p> <p>GLP</p>		<p>4,4'-sulphonyldiphenol</p> <p>Vehicle : 1 % CMC</p> <p>Conc. : 0, 100, 300 and 1000 mg/kg bw/d (in males the highest dose was changed to 600 mg/kg bw/d after 70 D)</p> <p>Duration of exposure : 90 days</p>	<p>Mortality : no animals died</p> <p>Clinical signs : soft and discoloured faeces and salivation in all animals exposed to the mid and high doses.</p> <p>Bw : sign. decreased in ♂ at the highest dose. The bwg (D 0-91) was significantly lower in ♂ in the mid and high dose level.</p> <p>Gross necropsy findings : dilatation of cecum in all ♂ of the high dose</p> <p>Enlarged liver in 8 ♀ at the high dose level</p> <p>Organ weight : sign. changes observed in both sexes (see table 34)</p> <p>Sign. lower ♂ reproductive organ weight (testes and epididymides)</p> <p>Histopathology : few changes (see table 35)</p> <p>Dilatation of cecum in all ♂ and ♀ at the highest dose + increase incidence of apoptosis</p> <p>Mammary glands : in ♂ : increased incidence of multifocal atrophy at the mid and high dose</p> <p>Uterus : increased incidence of squamous metaplasia</p>	<p>Anonymous 17, 2014</p>
<p>13-day repeated dose toxicity study</p> <p>Rat / strain not specified / male</p> <p>5 males/group</p> <p>Diet</p> <p>No guideline followed</p> <p>No GLP</p>		<p>4,4'-sulphonyldiphenol</p> <p>Vehicle : 1 % corn oil</p> <p>Doses : 0, 0.1 and 1 % (± 0, 97 and 810 mg/kg bw/d)</p> <p>Duration of exposure : 13 D</p>	<p>Bw : severely decreased at the highest dose (no further information available)</p> <p>Organ weight : lower kidneys and liver weights at 1 % (no further information available)</p> <p>Histopathology : adipose tissue atrophy and cytoplasmic basophilia of epithelium of the renal distal convoluted tubule at 1% (no further information available)</p>	<p>Anonymous 18, 1973</p>

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

No human data and other studies available

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

In a reproductive toxicity study (Anonymous 12, 2000), following OECD TG 421, groups of 12 male and 12 female rats were given 4,4'-sulphonyldiphenol via gavage at concentrations of 0, 10, 60 or 300 mg/kg bw/d. Males were exposed for a total of 45 days including 14 days of pre-mating period, through mating period to the day before necropsy. While, females were exposed for a total of 40 to 46 days (from mating period through gestation to lactation day 3).

Excessive salivation was observed just before or immediately after administration of the test substance in 7 males and 1 female exposed to the highest dose, however all of them recovered within 30 minutes after administration. The food consumption was examined during the pre-mating period (day 3, 7, 14), during the gestation and during the lactation. A statistically significant decrease of food consumption was only observed at day 3 of the pre-mating period in males and females at the high dose group (24.3 mg/kg bw/d vs 30.7 mg/kg bw/d in control group and 14.8 mg/kg bw/d vs 20.2 mg/kg bw/d in control group, respectively in males and females). The body weight was analyzed in males and females at the same time as food consumption examination. A statistically significant decreased body weight was noted in females at the highest dose at the end of the gestation period (see table 9).

Table 9 : body weight data (in g)

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

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

No abnormalities were observed in parental animals with regard to copulation index, parturition index, delivery index, number of corpora lutea and gestation period. However, an increased number of animals showed irregular oestrus cycle (5 females exposed to 300 mg/kg bw/d exhibited a longer dioestrus period of 6 to 10 days). The mean duration of oestrus cycle was significantly higher at the highest dose (see table 10). Most of the females, which had a continued dioestrus, were not fertilized and the fertility index decreased severely (58.3 % at the highest dose vs 91.7 % in control group). Furthermore, a declining tendency in the number of implantation sites and a significant decrease of implantation index were observed at the highest dose level.

Table 10 : reproductive performance

Dose level (mg/kg bw/d)	0	10	60	300
Nb of pairs	12	12	12	12
Mean oestrus cycle (in D)	4.08	4.01	4.14	5.57**
Inc of females with irregular oestrus cycle	0/12	0/12	1/12	5/12*
Fertility index (in %)	91.7	91.7	100.0	58.3

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

Table 11 : female reproduction delivery data

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

** : p<0.01

At necropsy, distension of the cecum was observed in 1 male and 1 female of the mid dose level and in all males (12) and 4 females of the highest dose group. The cecum examination revealed a significant increased incidence of diffuse hyperplasia of the mucosal epithelium and of single cell necrosis in males at 300 mg/kg bw/d. At the highest dose, the relative liver weight increased and a centrilobular hypertrophy of hepatocytes was observed in 5 males of the highest dose. In males and females, a tendency to decreased thymus weight was detected. Furthermore, in males, an increased relative pituitary weight and a decreased absolute seminal vesicle weight were observed.

Table 12 : organ weights

Dose level (mg/kg bw/d)	Males				Females			
	0	10	60	300	0	10	60	300
FBW (g)	513.4	517.3	526.7	488.1	360.1	354.1	333.0*	338.6
Pituitary (mg)	14.92	13.60	15.12	16.68	21.18	21.64	21.45	21.07
Pituitary rel. (*10 ⁻³)	2.89	2.63	2.88	4.43**	5.90	6.14	6.45	6.21
Thymus (mg)	289.6	336.3	332.1	254.5	263.1	312.7	253.5	221.7
Liver (g)	16.373	16.246	16.803	17.439	15.289	14.114	14.490	14.393
Liver rel.	3.185	3.135	3.185	3.562**	4.247	3.989	4.359	4.246
Testes (g)	3.559	3.480	3.554	3.503	-	-	-	-
Prostate (g)	0.723	0.746	0.777	0.708	-	-	-	-
Sem. ves. (g)	2.825	2.718	2.860	2.428**	-	-	-	-
Epididymis (g)	1.355	1.292	1.328	1.292	-	-	-	-
Ovaries (mg)	-	-	-	-	110.35	116.02	114.86	105.63
Uterus (g)	-	-	-	-	0.691	0.683	0.713	0.700

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

Table 13 : incidence of histopathological findings

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

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

Regarding offspring examination, see section 10.10.5.

In an extended-one generation reproductive toxicity study (Anonymous 13, 2019), performed following OECD TG 443, groups of male and female rats were given 4,4'-sulphonyldiphenol at a concentration of 0, 20, 60 and 180 mg/kg bw/d.

For the F0 parental generation, minimum 10 weeks after the beginning of exposure, 24 males and 24 females from the same dose group were mated. Shortly before weaning of the F1 pups, the F0 males were sacrificed whereas, the F0 females were sacrificed after weaning of the F1 pups. Before weaning of the F1 pups on PND 21, 74 animals/sex/group were randomly selected and, after weaning, placed into cohorts.

- Cohort 1A was composed of 20 males and 20 females per dose group and animals were sacrificed approximately when 13 weeks old.
- Cohort 1B was composed of 24 males and 24 females per dose group and was selected to produce F2 pups. As for the F0 parental generation, minimum 10 weeks after assignment of the F1 parental animals, males and females were mated. F1 males were sacrificed shortly before weaning and F1 females shortly after the weaning.
- Cohort 2A (neurotoxicity) was composed of 10 males and 10 females per dose group and animals were sacrificed approximately when 11 weeks old.
- Cohort 2B (neurotoxicity) was composed of 10 males and 10 females per dose group and animals were sacrificed approximately when 3 weeks old.
- Cohort 3 (immunotoxicity) was composed of 10 males and 10 females per dose group and animals were sacrificed approximately when 8-9 weeks old.
- Pups, which were not chosen for cohorts or for blood sampling on PND 4 and 22, were sacrificed after weaning.

F0 parental and F1 pups (before weaning):

Regarding the F0 parental generation, 1 female of the low dose group was sacrificed on study day 63 due to poor general condition. Thirteen males and 6 females exposed to 180 mg/kg bw/d exhibited transient salivation during the first weeks of exposure. However, the maternal care was not affected during gestation and lactation periods. Furthermore, a higher significant body weight value was only observed in females of the mid dose group at D 7 and 14 of the pre-mating period (pre-mating D 7 : 141.3, 144.8, 148.3* and 145.2g respectively at 0, 20, 60 and 180 mg/kg bw/d ; pre-mating D 14 : 162.8, 169.9, 172.4* and 169.6g respectively at 0, 20, 60 and 180 mg/kg bw/d).

Male reproduction parameters were examined and revealed a significant lower percentage of sperm motility (88, 84*, 85* and 86* % respectively at 0, 20, 60 and 180 mg/kg bw/d). Other parameters were not affected (total spermatids/gram testis, total sperms/gram cauda epididymis, % of abnormal sperms, male mating index and male fertility index).

Regarding female reproduction parameters, the mean oestrus cycle duration was significantly increased at the highest dose (see table 14). At 20 mg/kg bw/d, 1 female exhibited a mean oestrus length of 5.3 days and one other female had a mean cycle length of 4.0 days; however, this last female showed an oestrus cycle with a dioestrus period of 9 days. Two females exposed to 180 mg/kg bw/d exhibited a mean cycle length of 4.7 and 5.0 days. This last one had one cycle with a dioestrus period of 5 days. Fertility index (96, 91, 100 and 96 % respectively at 0, 20, 60 and 180 mg/kg bw/d) and duration of gestation (22.0 days in all groups) were not affected. However, a decreasing trend in the mean number of implantation sites was noted (15.3, 14.8, 14.9 and 14.3 respectively at 0, 20, 60 and 180 mg/kg bw/d).

Table 14 : oestrus cycle data

Dose level (in mg/kg bw/d)	0	20	60	180
Mean day from oestrus to oestrus (in day)	3.9	3.9	3.9	4.1*

Mean number of days in stage : prooestrus ^A	4.7	3.5	3.8	2.2
Mean number of days in stage : oestrus ^A	5.1	5.1	5.0	5.2
Mean number of days in stage : metoestrus ^A	5.8	6.0	5.8	5.9
Mean number of days in stage : dioestrus ^A	6.3	7.4	7.7	9.0

* : p<0.05

^A : Oestrus cycle data was generated during the last 3 weeks prior to mating. These mean were calculated by the DS

At necropsy, enlarged cecum and enlarged kidneys were observed in males of the highest dose (respectively in 3 males and in 6 males). Absolute and relative adrenal glands, kidneys and thymus weights were significantly modified in males and relative liver weight was significantly higher in females (see table 15).

Table 15 : Modified organ weights and microscopic findings

		Males				Females			
Dose level (in mg/kg bw/d)		0	20	60	180	0	20	60	180
FBW (in g)		521.575	514.408	521.35	507.229	272.125	278.826	275.429	273.408
Adrenal glands	Abs (mg)	54.0	55.958	58.75*	60.625*	80.208	70.391	77.208	71.625
	Rel	0.01	0.011	0.011*	0.012**	0.029	0.025	0.028	0.026
Kidneys	Abs (g)	3.543	3.391	3.673	4.124**	2.083	2.135	2.137	2.148
	Rel	0.68	0.663	0.705	0.817**	0.767	0.768	0.776	0.787
	Incidence (Inc.) of medullar mineralization	0	0	1	21	14	2	1	15
	Inc. of nuclear crowding	0	0	0	22	0	0	0	0
	Inc. of tubular dilatation	0	0	0	13	0	0	0	0
Liver	Abs (g)	12.572	13.298	13.003	12.46	8.08	8.259	8.348	8.695
	Rel	2.413	2.575	2.491	2.455	2.968	2.964	3.029	3.181**
Thymus	Abs (mg)	250.167	283.375	283.292*	233.708	239.167	224.391	233.625	218.875
	Rel	0.048	0.056	0.054*	0.046	0.088	0.081	0.085	0.08

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

Regarding offspring examination, the mean number of F1 pups per dam was lower at the mid and high doses. Moreover, the mean pup body weight was significantly higher at the 2 highest dose levels. For more information see section 10.10.5.

Cohort 1A :

1 female of the highest dose was found dead on study day 0 (necropsy revealed a slight fibrinous inflammation in the lung, focal hyperplasia in the mammary gland and an atrophic uterus). 12 males and 14

females of the highest dose exhibited transient salivation immediately after dosing. Body weight was significantly higher in females exposed to 60 and 180 mg/kg bw/d at D 14 and 28 (see table 16).

Table 16 : body weight data (in g)

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

* : p<0.05

Regarding reproduction parameters, sperm was examined and did not show any modification. In females, during the 2 weeks of observation, oestrus cycle was of 4.1 days in all groups, but showed prolonged dioestrus stage, as in the other cohorts observed (see table 17).

Table 17 : oestrus cycle data

Dose level (in mg/kg bw/d)	0	20	60	180
Mean day from oestrus to oestrus (in day)	4.1	4.1	4.1	4.1
Mean number of days in stage : prooestrus ^A	2.2	2.0	2.2	1.3
Mean number of days in stage : oestrus ^A	3.5	3.6	3.5	3.2
Mean number of days in stage : metoestrus ^A	3.8	3.9	3.6	4.1
Mean number of days in stage : dioestrus ^A	4.5	4.6	4.8	5.4

* : p<0.05

^A : Oestrus cycle data was generated during the last 3 weeks prior to mating. These mean were calculated by the DS

At the end of the exposure period (approximately 90 days), animals were sacrificed and necropsied. No macroscopic dose related findings were observed. Some organs exhibited weight differences (see table 18). As in the F0 parental generation histopathological changes were observed in kidneys (medullar mineralization, nuclear crowding and tubular dilatation). Moreover, an increased incidence in atrophy of mammary gland was observed at the highest dose (in 1, 0, 2 and 7 males respectively at 0, 20, 60 and 180 mg/kg bw/d).

Table 18 : organ weight changes

Dose level (in mg/kg bw/d)	Males				Females			
	0	20	60	180	0	20	60	180

FBW (g)		455.095	449.15	452.61	433.11	242.17	240.59	248.375	251.237
Adrenal glands	Abs (mg)	65.0	63.2	63.6	70.5	69.05	69.15	71.5	76.737
	Rel	0.014	0.014	0.014	0.016**	0.029	0.029	0.029	0.031
Kidneys	Abs (g)	3.224	3.137	3.335	3.599**	1.797	1.791	1.86	1.91
	Rel	0.712	0.701	0.737	0.832**	0.745	0.745	0.747	0.759
Liver	Abs (g)	13.032	13.349	12.923	11.265**	6.828	6.725	6.906	7.238
	Rel	2.863	2.973	2.858	2.601**	2.814	2.794	2.78	2.88
Spleen	Abs (g)	0.876	0.817	0.801*	0.726**	0.524	0.494	0.529	0.502
	Rel	0.194	0.182	0.177*	0.168**	0.216	0.206	0.213	0.2
Thymus	Abs (mg)	435.7	418.45	435.35	350.85*	354.05	356.75	381.8	355.158
	Rel	0.095	0.094	0.096	0.08	0.146	0.148	0.154	0.142
Prostate	Abs (g)	1.163	1.118	1.053*	1.046**	-	-	-	-
	Rel	0.257	0.252	0.233	0.242	-	-	-	-

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

Cohort 1B:

During the study period, 1 female of the mid dose group was found dead on pre-mating D 3 (histopathological examination not performed). Clinical observation revealed excessive salivation immediately after exposure to the test substance in 11 males and 9 females during the in-life period and in 10 females during gestation period. Significant body weight changes was observed in both sexes during the in-life period (see table 19 and 20).

Table 19: male body weight data (in g)

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

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

Table 20: female body weight data (in g)

Dose level (in mg/kg bw/d)		0	20	60	180
In-life period	D 0	73.4	71.5	75.4	73.6
	D 21	170.9	170.7	185.8**	184.7**

	D 49	237.6	233.0	252.7*	258.4**
	D 70	265.6	260.9	280.9	284.4*
Gestation period	GD 0	276.8	270.5	292.2	291.4
	GD 14	345.9	335.1	356.3	355.7
	GD 20	426.0	412.3	436.5	415.7
Lactation period	LD 0	330.6	323.8	343.8	341.3
	LD 10	359.3	350.6	371.4	367.0
	LD 21	342.3	332.9	356.6	353.0

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

Regarding reproduction data, fertility index was not affected (100, 100, 96, 96 % respectively at 0, 20, 60 and 180 mg/kg bw/d). However, a slightly reduced number of females with liveborn pups was observed at 60 and 180 mg/kg bw/d. The oestrus cycle was also modified at the highest dose level. Furthermore, the mean number of implantation sites tended to decrease at 180 mg/kg bw/d. (see table 21)

Table 21 : fertility data

Dose level (in mg/kg bw/d)	0	20	60	180
Female mating index (in %)	100	100	100	100
Mean mating day until DPC 0	3.0	2.4	2.5	3.0
Female fertility index (in %)	100	100	96	96
Nb of females with liveborn pups	24	24	21	21
Nb of females with stillborn pups	6	2	2	6
Mean day from oestrus to oestrus	3.9	4.0	4.0	4.5
Mean number of days in stage : prooestrus ^A	4.7	2.8	2.2	1.3
Mean number of days in stage : oestrus ^A	5.4	5.2	5.4	4.6
Mean number of days in stage : metoestrus ^A	6.0	6.0	6.3	5.9
Mean number of days in stage : dioestrus ^A	6.8	8.4	9.2	11.2
Mean nb of implantation sites	15.2	14.6	15.4	13.7
Duration of gestation (in day)	22.0	21.9	22.0	22.0

Statistical examination was not performed regarding the mean day of oestrus's stage ; ** : p<0.01

^A : Oestrus cycle data was generated during the last 3 weeks prior to mating. These mean were calculated by the DS

Shortly before weaning, parental animals were sacrificed. Necropsy revealed enlarged kidneys in 1 male of the mid dose and in 10 males of the highest dose. 3 organs showed weight modifications (see table 22). All other weight parameters did not show significant differences. Regarding the histopathological examination, an atrophy of the mammary gland was only noted in 1 male of each group.

Table 22 : organ weight data

Dose level (in mg/kg)	Males				Females			
	0	20	60	180	0	20	60	180

bw/d)									
FBW (g)		536.054	530.863	548.279	510.363	291.842	284.588	304.817*	308.2 ^A
Adrenal glands	Abs (mg)	59.792	62.625	67.708**	64.708	76.708	72.292	77.435	80.083
	Rel	0.011	0.012	0.012*	0.013**	0.026	0.026	0.025	0.026
Kidneys	Abs (g)	3.375	3.43	3.807**	4.252**	2.158	2.115	2.212	2.31*
	Rel	0.632	0.649	0.696**	0.832**	0.741	0.746	0.726	0.752
Liver	Abs (g)	14.813	15.395	14.677	13.272*	9.455	9.326	9.5	9.716
	Rel	2.758	2.902	2.669	2.6*	3.237	3.28	3.119	3.175

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

^A : S.d : 24.228, 20.968, 15.011 and 30.56, respectively at 0, 20, 60 and 180 mg/kg bw/d

Regarding offspring examination, the incidence of post-implantation loss and the number of liveborn pups were affected (for more information see section 10.10.5)

Cohort 2A :

No mortality occurred during the study period. As in the other cohorts, excessive salivation was observed immediately after exposure to the test substance in 3 males and 1 female of the highest dose. No body weight change was observed. In this cohort, neurotoxicity was examined. Auditory startle response, home cage observations, open field observations, sensorimotor tests/reflexes, motor activity measurement and learning and memory test did not show test-related effects.

Cohort 2B :

Necropsy examination did not reveal abnormalities.

Cohort 3 :

One female of the lowest dose was found dead on the study day 18. During the exposure period, clinical observation and body weight examination were not affected. No indication of toxicity of reproduction observed in this cohort. For developmental toxicity of the immune system, see section 10.10.5.

In a reproduction/developmental toxicity screening study (Anonymous 14, 2017), performed as a range finding study preceding the EOGRTS, groups of 10 male and 10 female rats were given 4,4'-sulphonyldiphenol at a concentration of 0, 30, 100 and 300 mg/kg bw/d. Animals were exposed for 10 w (for males : 6 w of pre-mating period, 2 w of mating period, and 4 w of post mating period ; and for females : 6 w of pre-mating period, 2 w of mating period, and continued through gestation and lactation periods).

No premature death occurred during the exposure period. At the highest dose, animals exhibited excessive salivation and a lower bw value (-7 % and -6 % respectively in males and females, compared to the control group).

Reproductive data were examined and revealed effects at the highest dose. Females exhibited prolonged oestrus cycle and pregnant females had a significantly lower mean number of implantation sites.

Table 23 : reproductive data

Dose level (in mg/kg bw/d)	0	30	100	300
Mean duration of oestrus cycle (d)	4.02	3.97	4.01	5.16**

Fertility index (%)	100	90	100	60
Mean nb of implantation sites	15.8	15.0	15.5	10.4**
Females without implantation sites	0	0	0	2
Mean duration of gestation (d)	22	22.1	22	22

* p<0.05 ; ** : p<0.01

Necropsy revealed treatment-related effects. Macroscopic examination revealed changes in males. Cecum was dilated in 3 males exposed to 300 mg/kg bw/d. Moreover, kidneys were discolored in 8 males and enlarged in 9 males of the highest dose and liver was enlarged in 1, 2 and 3 males respectively at 30, 100 and 300 mg/kg bw/d). Significant higher relative kidneys weight was observed in males (+ 11.5 and + 35 % respectively at 100 and 300 mg/kg bw/d) and significant higher relative liver weight was noted in males at the highest dose (+ 11 %) (see table 24). Furthermore, uterus weight was increased in females exposed to 300 mg/kg bw/d. Microscopic examination revealed also changes in these organs as well as in mammary gland in males (see table 25).

Table 24 : Organ weight data (in g)

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

* p<0.05 ; ** : p<0.01

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

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

Table 25 : microscopic data

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

Pups were recorded and examined. At the highest dose, the total number of pups delivered was reduced and the mean number of pups delivered was significantly lower. For more information see section 10.10.5

In a 28-day repeated dose toxicity study (Anonymous 15, 2017), performed as a range finding study preceding the EOGRTS, 5 male and 5 female rats were given 0, 100, 300 or 600 mg/kg bw/d of 4,4'-sulphonyldiphenol. Animals were exposed daily during 28 days.

A significantly lower bwg value was noted in males of the highest dose level (no further information available).

At the end of the exposure period, animals were sacrificed and examined. Males exhibited a significantly decreased FBW (-9 and -12 % respectively at 300 and 600 mg/kg bw/d, compared to control). Enlarged kidneys were noted in 3 males exposed to 300 mg/kg bw/d and in 4 males exposed to 600 mg/kg bw/d. The relative kidneys weight was higher at the mid and high dose in both sexes (+33 % and +12 % respectively in males and females, compared to the control group). Microscopic examination revealed also changes in kidneys. In 2, 5 and 5 males exposed respectively to 100, 300 and 600 mg/kg bw/d, minimal to moderate tubular degeneration/regeneration in kidneys was noted. Moreover, tubular hypertrophy was observed in 5 males of the highest dose (moderate hypertrophy), in 5 males of the mid dose (minimal hypertrophy) and in 1 male of the low dose (minimal hypertrophy). The relative adrenals weight was higher in males (+18 and +39 % respectively at 300 and 600 mg/kg bw/d, compared to the control group) and minimal hypertrophy/hyperplasia in the adrenal cortex was observed in 3 males exposed to 600 mg/kg bw/d. Liver exhibited also changes. The relative liver weight was increased in females (+9 and +12 % respectively at 300 and 600 mg/kg bw/d, compared to the control group). Centrilobular hypertrophy of the liver was noted in 1 males of the low dose (minimal hypertrophy), in 4 males of the mid dose (slight hypertrophy) and in all animals of the high dose (moderate hypertrophy in males and slight in females) (no further information available).

Examination of the reproductive organs revealed lower relative prostate and seminal vesicles weight at the highest dose (-15 % for prostate and -16 % for seminal vesicles). 3 males exposed to 300 mg/kg bw/d and 4 males exposed to 600 mg/kg bw/d exhibited diffuse atrophy of the mammary gland (no further information available).

In a 28-day repeated dose toxicity including 2-week observation of reversibility (Anonymous 16, 1999), performed similarly to OECD TG 407, main groups of 6 male and 6 female rats were given diets containing 4,4'-sulphonyldiphenol at a concentration of 0, 40, 200 and 1000 mg/kg bw/d during 28 days. Additionally of these main groups, recovery groups of 6 male and 6 female rats were given diets containing 4,4'-sulphonyldiphenol at a concentration of 0, 200 and 1000 mg/kg bw/d during 28 days and thereafter were observed during 2w.

During the dosing period, 2 males exposed to the highest dose died (1 after 13 D and 1 after 21 D). The clinical sign examination revealed an abdominal distension at the highest dose group in 1 female after 15 days of exposure and in 5 females after 28 days of exposure. During the recovery period, this effect disappeared.

Significant lower body weight values were recorded at the highest dose level in males during the dosing period. This significant reduction disappeared during the recovery period. In females, only a slight decrease was observed. However, the body weight gain (D 1–28) was significantly reduced at the highest dose in both sexes. (see table 26)

Table 26 : body weight data during dosing and recovery period (in g)

	Males	Females
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Dose level (mg/kg bw/d)	0	40	200	1000	0	40	200	1000
Exposure period								
D 1	217	214	215	215	165	165	166	168
D 14	330	324	325	281**	216	216	210	206
D 28	409	402	401	337**	258	256	244	240
BWG (1 – 28)	192	187	186	122**	93	91	78*	72**
Recovery period								
D 1	398	/	411	330**	258	/	250	242
D 14	457	/	465	416	286	/	278	269
BWG (1 – 14)	59	/	54	86**	28	/	58	27

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

Examination of the haematological and clinical chemistry parameters revealed significant changes (see table 27 and 28). Significant decrease of RBC, haemoglobin and haematocrit were observed in both sexes at the highest dose level and a significant reduced prothrombine time was noted in females. Furthermore, in males, a significant higher ALP activity and a significant lower LDH activity were noted at the highest dose level. Whereas, in females, a significant increase of total protein, albumin and calcium and a significant decrease of total cholesterol was observed.

Table 27 : haematological findings

		Males				Females			
Dose level (mg/kg bw/d)		0	40	200	1000	0	40	200	1000
Dosing period	RBC (10 ⁴ /mm ³)	770	764	763	687*	773	766	776	705**
	Hb (g/dL)	15.9	15.9	15.8	14.3**	16.2	15.9	15.9	13.9**
	Ht (%)	47	47	46	42**	47	47	47	42**
	MCHC (%)	34.1	33.9	34.1	33.7	34.5	34.0*	33.9*	33.6*
	PT (sec)	12.9	13.4	13.6	12.9	12.0	12.2	12.0	11.4*
Recovery period	RBC (10 ⁴ /mm ³)	804	/	793	735**	809	/	801	762
	Hb (g/dL)	16.0	/	15.9	15.3	16.2	/	15.8	15.2**
	Ht (%)	47	/	47	45	47	/	47	45
	MCHC (%)	33.8	/	33.9	33.8	34.1	/	33.3*	33.4
	PT (sec)	13.5	/	13.2	11.8**	11.9	/	11.6	11.7

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

Table 28 : blood chemical findings

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

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

Concerning the gross pathological observation, in cases where animals are necropsied at the end of the dosing period, a dilatation of cecum was observed in all animals of the highest dose level (5 out of 5 males and 6 out of 6 females at 1000 mg/kg bw/d). This change is not observed in the other dose level groups and in the control group. Whereas, in cases where animals are necropsied at the end of the recovery period, dark red spots in the glandular stomach were observed in 2 females of the mid dose level and 2 females of the high dose level. No abnormalities were seen in males necropsied at the end of the recovery period.

Regarding the organ weight examination, animals necropsied at the end of dosing period showed, at 1000 mg/kg bw/d, significant changes of absolute thymus and lung weights in both sexes and significant changes of absolute heart and adrenal glands weights in males (See table 29). While, animals necropsied at the end of recovery period exhibited, at 1000 mg/kg bw/d, significant higher absolute adrenal glands weight in males (59, 60 and 80** mg respectively at 0, 200 and 1000 mg/kg bw/d), significant higher relative kidneys weight in males and females (0.70/0.65, 0.73/0.75** and 0.81**/0.72* respectively in females/males at 0, 200 and 1000 mg/kg bw/d), significant higher relative liver weight in females (2.79, 2.82 and 3.21* respectively at 0, 200 and 1000 mg/kg bw/d).

Table 29 : absolute and relative organ weights data of animals necropsied at the end of dosing period

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

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

Weight (absolute and/or relative) of adrenals, liver and thymus were modified. These organs were also affected at the histological level. Furthermore, cecum examination revealed a hyperplasia of the mucosa and single cell necrosis of the mucosal epithelium at 200 and 1000 mg/kg bw/d. Whereas, the histopathological examination of animals necropsied at the end of the recovery period revealed significant changes in femur (increase spongy bone in 4* females at 1000 mg/kg bw/d), in spleen (significant increase of extramedullary haematopoiesis). Moreover, hyperplasia of cecum mucosa was observed in 3 males and in 1 female at the highest dose level (vs in 0 males and in 0 females in control group). (See table 30)

Table 30 : histopathological findings in animals necropsied at the end of the dosing period

		Males				Females				
Dose level		0	40	200	1000	0	40	200	1000	
Main groups										
Cecum	Hyperplasia mucosa	P	0/6	0/6	6*/6	5*/5	0/6	0/6	5**/6	6**/6
		Slight			2	2			4	5
		Mild			4	3			1	1
	Single cell necrosis, mucosal epithelium	P	0/6	0/6	4*/6	5*/5	0/6	0/6	4*/6	4*/6
		Slight			3	2			4	1
		Mild			1	3				2
	Moderate								1	
Liver	Hypertrophy centrilobular	P	0/6	0/6	0/6	3*/5	0/6	0/6	0/6	3/6
		Slight				3				3
Adrenals	Hypertrophy, zona fasciculata	P	0/6	0/6	0/6	4*/5	0/6	0/6	0/6	0/6
		Slight				4				
Thymus	atrophy	P	0/6	0/6	0/6	4**/5	0/6	0/6	0/6	4*/6
		Slight				4				4
Femur	Increase spongy bone	P	0/6	0/6	0/6	5**/5	0/6	0/6	0/6	4*/6
		Slight				5				4
Spleen	Haematopoeisis, extramedullary	P	6/6	6/6	6/6	5/5	0/6	0/6	6/6	6/6
		Slight	6	5	5	2			5	4
		Mild		1	1	2			1	2
		Moderate				1				
Recovery groups										
Cecum	Hyperplasia, mucosa	P	0/6	/	1/6	3/5	0/6	/	1/6	1/6
		Slight				1				1
		Mild			1	2			1	
Femur	Increase spongy bone	P	0/6	/	0/6	1/5	0/6	/	0/6	4*/6
		Slight				1				4
Spleen	Haematopoeisis extramedullary	P	6/6	/	6/6	5**/5	6/6	/	6/6	6*/6
		Slight	3		2		5		5	1
		Mild	3		4		1		1	3
		Moderate				5				2

* : p < 0.05 ; ** : p < 0.01 ; P : present

In a 90-day repeated dose toxicity study similar to OECD TG 408 (Anonymous 17, 2014), groups of 10 male and 10 female rats were exposed via gavage to 4,4'-sulphonyldiphenol at a concentration of 0, 100, 300 or 1000 mg/kg bw/d. The group of male rats receiving 1000 mg/kg bw/d was changed to 600 mg/kg bw/d onwards 70 days.

The animals of the 2 highest dose presented soft and discoloured faeces and excessive salivation. The body weight decreased in males at the mid dose level and was significantly lower in males at the highest dose. Furthermore, the body weight gain reduced significantly in males at the 2 highest dose levels. (See table 31)

Table 31 : body weight and body weight gain examination (in g)

Dose level (mg/kg bw/d)	Males				Females			
	0	100	300	1000/600	0	100	300	1000
D 0	158.4	157.1	158.1	158.2	126.1	127.0	126.0	126.7
D 42	351.4	343.8	326.0	293.3**	208.4	204.7	202.8	205.2
D 91	417.1	400.7	377.3	334.7**	237.3	231.7	225.0	222.5
BWG (D 0-91)	258.7	243.6	219.2*	176.4**	111.2	104.6	99.0	95.9

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

Blood examination revealed significant haematological changes and significant modification of enzymes. RBC and haemoglobin were significantly lower at the highest dose in both sexes. Other changes were observed however not in both sexes. (see table 32 and 33)

Table 32 : haematological findings (examined at the end of the administration period)

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

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

Table 33 : enzyme data (examined at the end of the administration period)

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

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

^A : S.d : 0.12, 0.47, 0.16 and 0.46, respectively at 0, 100, 300 and 1000/600 mg/kg bw/d

At necropsy, a dilatation of cecum was observed in all males exposed to 1000 mg/kg bw/d of 4,4'-sulphonyldiphenol, while the liver was enlarged in 8 females out of 10 at this dose level. An uterus dilatation was also observed in 3 females at the mid dose level. After this external examination, the organ weight was recorded and revealed a significant reduction of the male reproductive organs. Moreover, significant lower brain and thymus weights were observed in both sexes at the highest dose whereas a higher adrenal glands weight was noted. (See table 34)

Table 34 : organ weight (relative weight in %)

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

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

Concerning the histopathological examination, changes were observed in organs such as cecum, kidneys, liver, mammary gland, spleen and uterus. In spleen, an extramedullary haematopoiesis was observed in both sexes at 1000 mg/kg bw/d. Furthermore, changes in cecum were observed particularly in the highest dose level in both sexes. Squamous metaplasia in uterus was observed in all tested dose level. Moreover in females, modification in liver (centrilobular hypertrophy and cellular alteration) were observed in all tested dose level, while in males, a multifocal atrophy was noted in mammary gland at the 2 highest dose levels and a hypertrophy/hyperplasia of the adrenal cortex was noted at 1000 mg/kg bw/d.

Table 35 : incidence of histopathological findings

			Males				Females			
Dose level (mg/kg bw/d)		Grade	0	100	300	1000/600	0	100	300	1000
Adrenal cortex	Hypertrophy/hyperplasia	P	0/10	0/10	0/10	8/10	0/10	0/10	0/10	0/10
Cecum	Dilatation	P	0/10	0/10	0/10	10/10	0/10	0/10	1/10	10/10
	Parasite(s) in lumen	P	0/10	0/10	0/10	1/10	0/10	0/10	0/10	0/10
	Increased apoptosis (all of grade 1)	P	0/10	3/10	4/10	7/10	0/10	1/10	4/10	7/10
Kidneys	Mineralization, medulla	P	0/10	7/10	9/10	6/10	5/10	NE	NE	3/10
		1	-	4	6	6	-	-	-	-
		2	-	3	2	-	-	-	-	-
		3	-	-	1	-	-	-	-	-
	Tubules, basophilic	P	8/10	8/10	9/10	8/10	2/10	NE	NE	3/10
Liver	Centrilobular hypertrophy	P	0/10	0/10	0/10	0/10	0/10	2/10	5/10	10/10
		1	-	-	-	-	-	1	1	0
		2	-	-	-	-	-	1	3	0
		3	-	-	-	-	-	-	1	10
	Hyperplasia, bile duct	P	0/10	0/10	0/10	0/10	0/10	0/10	0/10	2/10
	Cellular alteration	P	0/10	1/10	0/10	2/10	1/10	1/10	1/10	6/10
Mammary gland	Atrophy multifocal	P	0/10	0/10	7/10	10/10	0/10	NE	NE	0/10
		1	-	-	7	0	-	-	-	-
		2	-	-	-	4	-	-	-	-
		3	-	-	-	2	-	-	-	-
		4	-	-	-	3	-	-	-	-
		5	-	-	-	1	-	-	-	-
Spleen	Haematopoeisis extramedullary	P	0/10	0/10	0/10	8/10	2/10	1/10	4/10	10/10
		1	-	-	-	5	2	1	4	3
		2	-	-	-	3	-	-	-	7
Uterus	Squamous metaplasia	P	-	-	-	-	0/10	2/10	2/10	5/10
		1	-	-	-	-	-	2	2	4
		2	-	-	-	-	-	-	-	1
		Dilatation of horn(s)	P	-	-	-	-	0/10	0/10	3/10

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

In a 13-day repeated dose toxicity study not performed according to an OECD guideline (Anonymous 18, 1973), groups of 5 male rats were given diets containing 4,4'-sulphonyldiphenol at a concentration of 0, 0.1 or 1 % (corresponding to 0, 97 and 810 mg/kg bw/d).

Body weight was severely depressed at the highest dose level (no further information available). Blood examination revealed a slight increase in RBC count, haemoglobin concentration and haematocrit and a lower aspartate aminotransferase value at the highest dose. Moreover, a slight increase in haemoglobin concentration was already observed at the low dose level (no further information available).

At necropsy, an adipose tissue atrophy was observed in 1 male at 0.1 % and in all males at 1 %. The organ weight recording revealed a lower absolute liver and kidneys weights at the highest dose level. The adipose tissue atrophy was confirmed at the histopathological examination. Moreover, a cytoplasmatic basophilia of epithelium of the renal distal convoluted tubule was noted at 1 % (no further information available).

10.10.3 Comparison with the CLP criteria

Criteria for Category 1	Criteria for category 2
<p>“Known or presumed human reproductive toxicant</p> <p>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 (category 1A) or from animal data (category 1B).</p> <p>Category 1A : known human reproductive toxicant. The classification is largely based on evidence from humans</p> <p>Category 1B : presumed human reproductive toxicant. The classification 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 non-specific 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.”</p>	<p>“Suspected human reproductive toxicant</p> <p>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.</p> <p>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.”</p>

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

4,4'-sulphonyldiphenol consistently and severely disturbed reproductive parameters such as the number of implantation sites and the oestrus cycle.

The mean number of implantation sites was reduced by 33 % in females exposed to 300 mg/kg bw/d in the reproductive toxicity study (Anonymous 12, 2000) (10.7 vs 15.9 in the control group). The implantation index at the same dose level, in this study, was 64.89** % vs 95.80 % in the controls. The same reduction in the mean number of implantation sites was also observed in the combined repeated dose toxicity study with the reproduction/developmental screening test (Anonymous 14, 2017), with 10.4** vs 15.8 at 300 and 0 mg/kg bw/d, respectively.

In the EOGRTS (Anonymous 13, 2019), the number of implantation sites was moderately modified only in the cohort 1B (13.7 vs 15.2 at 180 and 0 mg/kg bw/d, respectively). However, the DS wants to highlight that this effect appeared at a much lower dose than in Anonymous 12 (2000) and in Anonymous 14 (2017).

Regarding the oestrus cycle, at 300 mg/kg bw/d, a significant increase in the mean duration of the oestrus cycle (5.57 ** vs 4.08 days in the control group) was observed in the reproductive toxicity test (Anonymous 12, 2000). Furthermore, in the same study, 5 females out of 12 showed a prolonged dioestrus period (6-10

days) and 4 out of 5 did not conceive at all, leading to a severely reduced fertility index in the highest dose group (58.3 % vs 91.7 % in the control group).

In the EOGRTS (Anonymous 13, 2019), the mean duration of the oestrus cycle in the parental generation was significantly increased at 180 mg/kg bw/d (4.1* vs 3.9 days in the control group). Also, as observed in Anonymous 12 (2000), the mean dioestrus period was increased in the highest dose group (9.0 at 180 mg/kg bw/d vs 6.3 days in the controls). The cohort 1B exhibited the same trend as the mean duration of the oestrus cycle was increased at the highest dose (4.5 d vs 3.9 d in the controls) and the mean number of days in dioestrus was also prolonged (11.8 d vs 6.8 d at 180 mg/kg bw/d and in controls, respectively). The mean duration of oestrus cycle was not prolonged during the short observation period of cohort 1A, but the same trend prolongation in dioestrus was also observed (5.4 vs 4.3 days at 180 mg/kg bw/d and in the control group, respectively).

Furthermore, in Anonymous 14 (2017), a significant increase in the mean duration of oestrus cycle was observed at the highest dose (5.16** d at 300 mg/kg bw/d vs 4.02 d in controls).

All these severe effects cannot be explained by maternal toxicity as general condition of the animals was unaffected by the treatment in all studies. Animals only exhibited excessive salivation just before or immediately after exposure to the test substance in all studies. Moreover, body weight examination showed only slight variations during the premating and mating periods that cannot be accounted for these effects.

Severe decreased number of implantation sites and severe higher oestrus duration were observed in three different studies. These effects were more pronounced in the reproductive toxicity test (Anonymous 12, 2000) and in the combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (Anonymous 14, 2017). In the EOGRTS (Anonymous 13, 2019), the highest tested dose was only 180 mg/kg bw/d (compared to 300 mg/kg bw/d in Anonymous 12 (2000) and Anonymous 14 (2017)). At this top dose, nearly absent general toxicity was observed. The DS wants to highlight that females exposed to 180 mg/kg bw/d exhibited already significant fertility effects which would be more pronounced if the study would have been dosed higher as it is the case in the Anonymous 12 (2000) and Anonymous 14 (2017).

According to the CLP criteria a classification as Repr. 1B for adverse effects on sexual function and fertility is warranted based on the above mentioned severe effects observed in the available studies, which cannot be related to a general toxicity.

10.10.4 Adverse effects on development

Table 36: Summary table of animal studies on adverse effects on development

Method, species, no/group	guideline, strain, sex,	Test substance, dose levels duration of exposure	Results	Reference
Prenatal developmental toxicity study rat / wistar 25 pregnant females/group Gavage Following OECD TG 414 GLP		4,4'-sulphonyldiphenol Vehicle : 1 % CMC Dose : 0, 30, 100 and 300 mg/kg bw/d Exposure : gestational day (GD) 6 to 19 Sacrificed at GD	<u>Dams :</u> Clinical signs : excessive salivation noted in 7 out of 25 females exposed to 300 mg/kg bw/d Bw : no sign change (however bwg GD 6 – 19 and GD 8 - 10 were sign lower) Uterus weight : no effects Necropsy observation : no treatment-related effects Reproduction data (nb of dams with viable foetuses, corpora lutea, implantation sites, pre and post implantation loss, resorption) : no effects	Anonymous 19, 2014

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Method, species, no/group	guideline, strain, sex,	Test substance, dose levels of duration of exposure	Results	Reference
		20	<p><u>Offsprings :</u></p> <p>Sex ratio : unaffected</p> <p>Mean nb of live foetuses : no effects</p> <p>Bw : unaffected</p> <p>A few skeletal variations observed</p>	
<p>Reproductive toxicity test</p> <p>Rats / Spargue-Dawley (SD)</p> <p>12/sex/group</p> <p>Gavage</p> <p>Following OECD TG 421</p> <p>GLP</p>		<p>4,4'-sulphonyldiphenol</p> <p>Vehicle : 0.5 % aqueous sodium CMC solution with 0.1 % Tween 80</p> <p>Doses : 0, 10, 60 and 300 mg/kg bw/d</p> <p>Exposure : a total (tot.) of 45 D for males (including 14 D of pre-mating period, through mating to the day before necropsy) and a total of 40 to 46 D for females (from pre-mating, mating, gestation until lactation day (LD) 3) (females without delivery were exposed until D 25 after confirmation of copulation)</p>	<p><u>Parental generation :</u></p> <p>Clinical signs : excessive salivation at 300 mg/kg bw/d</p> <p>Bw : reduced at the highest dose in both sexes (see table 9)</p> <p>Gross necropsy findings : distension of cecum observed in 1 male (♂) and 1 female (♀) in the mid dose level and in all ♂ and 4 ♀ at the highest dose level</p> <p>Organ weight : in ♂ : sign. increase of relative (rel.) pituitary and rel. liver weights and sign. decrease of seminal vesicle weight</p> <p>In ♀ : no sign. changes at the highest dose observed</p> <p>Histopathology : cecum : sign. increased incidence of hyperplasia of the mucosal epithelium (in 11 ♂) and sign. higher incidence of single cell necrosis (in 5 ♂) at the highest dose</p> <p>Liver : centrilobular hypertrophy of hepatocytes observed in 5 ♂ at 300 mg/kg bw/d</p> <p><u>Offspring :</u></p> <p>Decreased mean nb of offspring at birth at 300 mg/kg bw/d (9.1 at 300 mg/kg bw/d vs 14.3 in control group)</p> <p>No abnormalities in external appearance and clinical signs nor bw, bwg, viability index, ano-genital distance (AGD)</p>	<p>Anonymous 12, 2000</p>
<p>EOGRTS with F2, DNT (cohorts 2A and 2B) and DIT (cohort 3)Rats / SD</p> <p>F0 generation : 24/sex/dose</p> <p>F1 generation : 20/sex/dose for cohort 1A, 24/sex/dose for cohort 1B, 10/sex/dose for cohorts 2A, 2B and 3</p> <p>Gavage</p> <p>Following OECD TG 443</p> <p>GLP</p>		<p>4,4'-sulphonyldiphenol</p> <p>Vehicle : 0.5 % CMC</p> <p>Doses : 0, 20, 60 and 180 mg/kg bw/d</p> <p>Duration of exposure : Minimum 10 w after the beginning of exposure, males and females from the same dose</p>	<p><u>Parental generation :</u></p> <p>Bw : sign. higher only in ♀ during the in-life period</p> <p>Mean nb of implantation site : reduced at the highest dose (14.3 vs 15.3 in control)</p> <p>Mean nb of post-implantation loss sign. affected (1.5** vs 0.5 in control)</p> <p>Necropsy : enlarged cecum and changes in kidneys observed in ♂ at 180 mg/kg bw/d</p> <p><u>F1 pups :</u></p> <p>Sign. lower tot. nb. of liveborn (285* at 180 mg/kg bw/d vs 340 in control) and sign. higher nb of stillborn (8* at 180 mg/kg bw/d vs 2 in control)</p> <p><u>Cohort 1A :</u></p>	<p>Anonymous 13, 2019</p>

Method, species, no/group	guideline, strain, sex, Test substance, dose levels duration of exposure	Results	Reference
	<p>group were mated. Shortly before weaning of the F1 pups, the F0 males were sacrificed whereas, the F0 females were sacrificed after weaning of the F1 pups. Before weaning of the F1 pups on PND 21, 74 animals/sex/group were randomly selected and, after weaning, placed into cohorts.</p>	<p>FBW : slightly reduced at 180 mg/kg bw/d in ♂</p> <p>BW : in ♀, body weight was sign. higher at D14 and D28 in the mid and high dose groups</p> <p>Necropsy : adrenal glands, kidneys, liver, spleen, thymus and prostate showed a significant deviation in abs. or rel. value</p> <p>An atrophy of the mammary gland was noted in ♂ of the highest dose</p> <p><u>Cohort 1B :</u></p> <p>Lower mean nb of implantation sites and sign. higher incidence of post-implantation loss at 180 mg/kg bw/d</p> <p>Necropsy : FBW slightly reduced in ♂ at the highest dose and a few organ weights modified</p> <p><u>Cohort 2A :</u></p> <p>Auditory startle response, home cage observations, open field observations, sensorimotor tests/reflexes, motor activity measurements and learning and memory tests : unaffected</p> <p><u>Cohort 2B :</u></p> <p>Necropsy examination : no effects observed</p> <p><u>Cohort 3 :</u></p> <p>Clinical and bw examination : unaffected</p> <p>Necropsy : sign lower rel. thymus weight at 180 mg/kg bw/d</p> <p>T-cell dependent antibody response : slight change in the low and mid dose in ♀</p> <p><u>F2 pups :</u></p> <p>Decrease tot. nb of pups delivered at the highest dose</p>	
<p>Range finding study preceding the EOGRTS, Similar to a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test</p> <p>Rats / SD 10/sex/dose</p> <p>Gavage</p> <p>Similar to OECD TG 422</p> <p>GLP</p>	<p>4,4'-sulphonyldiphenol</p> <p>Vehicle : CMC</p> <p>Doses : 0, 30, 100 and 300 mg/kg bw/d</p> <p>Duration of exposure : 10w for males and continued through pre mating, gestation, and lactation periods for females</p>	<p><u>F0 generation :</u></p> <p>Mortality : no premature death</p> <p>Clinical signs : excessive salivation observed at the highest dose</p> <p>Bw : lowered at the highest dose (-7 % in ♂ and -6 % in ♀ compared to the control group)</p> <p>Haematology and clinical biochemistry : no effects (no further information available)</p> <p>Gross pathological findings : increased incidence of cecum dilatation, enlarged and discoloration of kidneys and enlarged liver in ♂ exposed to 300 mg/kg bw/d</p> <p>Organ weight : sign. higher rel. kidneys weight in ♂ (+11.5 and +35 % respectively at 100 and 300 mg/kg bw/d) and sign higher rel. liver weight in ♂ at the highest dose (+11 %). In ♀, uterus weight modified at</p>	<p>Anonymous 14, 2017</p>

Method, species, no/group	guideline, strain, sex,	Test substance, dose duration of exposure	Results	Reference
			300 mg/kg bw/d Histopathology : changes observed in kidneys in both sexes. Furthermore, mammary gland and cecum also affected in ♂ % of post-implantation loss : sign. higher at 300 mg/kg bw/d (34.6* vs 3.6 % in control group) <u>F1 :</u> Mean nb of pups delivered sign decreased at the highest dose (10.8** vs 15.2) Pups bw sign. higher in ♂ of the low dose at PND 21 (+6.6 % compared to the control group) (no further information available) Gross pathological findings : no effects observed (no further information available)	

No human data or other studies available

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

In a prenatal developmental toxicity study following OECD TG 414 (Anonymous 19, 2014), groups of 25 pregnant rats were given 4,4'-sulphonyldiphenol via gavage at a concentration of 0, 30, 100 or 300 mg/kg bw/d. The animals were exposed to the test substance from gestational day 6 to 19 and were sacrificed at gestational day 20.

No mortality was noted during the exposure period. Furthermore, the clinical examination revealed only an increased incidence of females with excessive salivation. However, the maternal care was not affected. No significant body weight change was observed during the dosing period. However, the body weight gain value for GD 6 – 19 and GD 8 - 10 were significantly decreased at the highest dose (see table 37).

Table 37 : body weight data (in g)

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

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

For dams, no test substance-related changes were observed for the gravid uterus weight (59.1, 59.6, 58.7 and 55.8 g respectively at 0, 30, 100 and 300 mg/kg bw/d), neither for the necropsy observation nor for the reproduction data parameters (see table 38).

Table 38 : reproductive data

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

The foetus examination revealed no differences in sex distribution, placental weight and foetal body weight compared to the control group (see table 39). Skeletal variations were observed in all doses. At 300 mg/kg bw/d, these variations were significant however comprised within the range of the historical control data (see table 40). No treatment-related external malformation and variation nor soft tissue malformation and variation were observed.

Table 39 : sex ratio and mean foetal weight (in g)

Dose level (mg/kg bw/d)	0	30	100	300
Sex ratio (in % females/males)	48.9/51.1	47.2/52.8	56.6/43.4	47.3/52.7
Mean placental weight	0.45	0.46	0.45	0.47
Mean weight of all viable foetuses	3.6	3.6	3.4	3.4
Mean weight of male foetuses	3.6	3.7	3.5	3.5
Mean weight of female foetuses	3.5	3.5	3.4	3.3

Table 40 : skeletal variations data

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

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

In a reproductive toxicity study (Anonymous 12, 2000), following OECD TG 421, groups of 12 male and 12 female rats were given 4,4'-sulphonyldiphenol via gavage at concentrations of 0, 10, 60 or 300 mg/kg bw/d. Males were exposed for a total of 45 days including 14 days of pre-mating period, through mating period to the day before necropsy. While, females were exposed for a total of 40 to 46 days (from mating period through gestation to lactation day 3).

Excessive salivation was observed just before or immediately after administration of the test substance, however all animals recovered within 30 minutes after administration. A statistically significant decrease of food consumption was only observed at day 3 of the pre-mating period in males and females at the high dose group (24.3 mg/kg bw/d vs 30.7 mg/kg bw/d in control group and 14.8 mg/kg bw/d vs 20.2 mg/kg bw/d in control group, respectively in males and females). Furthermore, a statistically significant decreased body weight was noted in females at the highest dose at the end of the gestation period (see table 9 in section 10.10.2).

At necropsy, distension of the cecum was observed. The cecum examination revealed a significant increased incidence of diffuse hyperplasia of the mucosal epithelium and of single cell necrosis in males at 300 mg/kg bw/d. At the highest dose, the relative liver weight increased and a centrilobular hypertrophy of hepatocytes was observed in 5 males of the highest dose. In males and females, a tendency to decreased thymus weight was detected. Furthermore, in males, an increased relative pituitary weight and a decreased absolute seminal vesicle weight were observed. For more detail, see section 10.10.2.

Regarding offspring examination, a tendency to decrease in the total number of offspring at birth, number of live offspring at birth and number of live offspring on day 4 of lactation were observed in the highest dose group (see table 41). However, no significant difference in live birth index and viability index were noted (at PND 0 : 99.35, 100.00, 99.48 and 100.00 % respectively at 0, 10, 60 and 300 mg/kg bw/d and at PND 4 : 99.30, 95.45, 99.48 and 100.0 % respectively at 0, 10, 60 and 300 mg/kg bw/d). External examination did not reveal any clinical signs, body weight change (see table 42), nor anogenital distance modification. Furthermore, no abnormalities were observed in dead offspring on lactation day 0 to 4 and live offspring on lactation day 4 in each group.

Table 41 : mean number of pups

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

Table 42 : pups body weight data (in g)

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

In an extended-one generation reproductive toxicity study (Anonymous 13, 2019), performed following OECD TG 443, groups of male and female rats were given 4,4'-sulphonyldiphenol at a concentration of 0, 20, 60 and 180 mg/kg bw/d.

For the F0 parental generation, minimum 10 weeks after the beginning of exposure, 24 males and 24 females from the same dose group were mated. Shortly before weaning of the F1 pups, the F0 males were sacrificed whereas, the F0 females were sacrificed after weaning of the F1 pups. Before weaning of the F1 pups on PND 21, 74 animals/sex/group were randomly selected and, after weaning, placed into cohorts.

- Cohort 1A was composed of 20 males and 20 females per dose group and animals were sacrificed approximately when 13 weeks old.
- Cohort 1B was composed of 24 males and 24 females per dose group and was selected to produce F2 pups. As for the F0 parental generation, minimum 10 weeks after assignment of the F1 parental animals, males and females were mated. F1 males were sacrificed shortly before weaning and F1 females shortly after the weaning.
- Cohort 2A (neurotoxicity) was composed of 10 males and 10 females per dose group and animals were sacrificed approximately when 11 weeks old.
- Cohort 2B (neurotoxicity) was composed of 10 males and 10 females per dose group and animals were sacrificed approximately when 3 weeks old.
- Cohort 3 (immunotoxicity) was composed of 10 males and 10 females per dose group and animals were sacrificed approximately when 8-9 weeks old.
- Pups, which were not chosen for cohorts or for blood sampling on PND 4 and 22, were sacrificed after weaning.

F0 parental and F1 pups (before weaning):

Regarding the F0 parental generation, 1 female of the low dose group was sacrificed on study day 63 due to poor general condition. Thirteen males and 6 females exposed to 180 mg/kg bw/d exhibited transient salivation during the first weeks of exposure. However, the maternal care was not affected during gestation and lactation periods. Furthermore, a higher significant body weight value was only observed in females of the mid dose group at D 7 and 14 of the pre-mating period.

The mean number of post-implantation loss and the mean percentage of post implantation loss were significantly higher in the mid and high dose groups (see table 43). The average litter size was dose-dependently reduced (14.9, 14.0, 13.5 and 12.7 pups/dam respectively at 0, 20, 60 and 180 mg/kg bw/d).

Table 43 : post implantation data

Dose level (in mg/kg bw/d)	0	20	60	180
Mean number of post-implantation loss	0.5	0.8	1.3*	1.5**
Mean % of post-implantation loss	3.1	5.9	9.4*	10.5**

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

At necropsy, enlarged cecum and enlarged kidneys were observed in males of the highest dose (respectively in 3 males and in 6 males). Absolute and relative adrenal glands, kidneys and thymus weights were significantly modified in males and relative liver weight was significantly higher in females. For more detail, see section 10.10.2

Regarding offspring examination, due to the higher resorptions, the mean number of F1 pups per dam was lower in all tested groups and was dose related (14.9, 14.0, 13.5, 12.7 respectively at 0, 20, 60 and 180 mg/kg bw/d). Furthermore, the number of liveborn pups was significantly reduced at the highest dose (340, 289, 322 and 285* pups respectively at 0, 20, 60 and 180 mg/kg bw/d) and the number of stillborn pups was also significantly increased at the highest dose (2, 5, 3 and 8* pups respectively at 0, 20, 60 and 180 mg/kg bw/d). Moreover, the mean pup body weight was significantly higher at the 2 highest dose levels (see table 44). Sex ratio, clinical observations, viability index, anogenital distance, vaginal opening, preputial separation and presence of areolas/nipples were not modified by exposure to the test substance.

Table 44 : pup body weight data (in g)

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

* : p<0.05

^A : S.d : 0.52, 0.76, 0.74 and 0.76Cohort 1A :

1 female of the highest dose was found dead on study day 0 (necropsy revealed a slight fibrinous inflammation in the lung, focal hyperplasia in the mammary gland and an atrophic uterus). 12 males and 14 females of the highest dose exhibited transient salivation immediately after dosing. Body weight was significantly higher in females exposed to 60 and 180 mg/kg bw/d at D 14 and 28 (see table 16).

At the end of the exposure period (approximately 90 days), animals were sacrificed and necropsied. No macroscopic dose related findings were observed. Some organs exhibited weight differences (see table 18). As in the F0 parental generation histopathological changes were observed in kidneys (medullar mineralization, nuclear crowding and tubular dilatation). Moreover, an increased incidence in atrophy of mammary gland was observed at the highest dose (in 1, 0, 2 and 7 males respectively at 0, 20, 60 and 180 mg/kg bw/d).

Cohort 1B :

During the study period, 1 female of the mid dose group was found dead on pre-mating D 3 (histopathological examination not performed). Clinical observation revealed excessive salivation immediately after exposure to the test substance in 11 males and 9 females during the in-life period and in 10 females during gestation period. Significant body weight changes were observed in both sexes during the in-life period (see table 19 and 20).

Regarding female reproduction data, the mean number of implantation sites tended to decrease at 180 mg/kg bw/d and the mean number of post-implantation loss was significantly increased at the highest dose. (see table 45)

Table 45 : female reproduction data

Dose level (in mg/kg bw/d)	0	20	60	180
Nb of females with liveborn pups	24	24	21	21
Nb of females with stillborn pups	6	2	2	6
Mean nb of implantation sites	15.2	14.6	15.2	13.7
Tot. nb of post-implantation loss	22	18	25	76
Mean nb of post-implantation loss	0.9	0.8	1.1	3.3**
% of post-implantation loss	6.4	5.3	11.1	24.6**
Duration of gestation (in day)	22.0	21.9	22.0	22.0
Mean nb of pups delivered	14.3	13.8	14.9	11.4**

** : p<0.01

Shortly before weaning, parental animals were sacrificed. Necropsy revealed enlarged kidneys in 1 male of the mid dose and in 10 males of the highest dose. 3 organs showed weight modifications (adrenal glands, kidneys and liver see table 22). All other weight parameters did not show significant differences. Regarding the histopathological examination, an atrophy of the mammary gland was only noted in 1 male of each group.

Regarding offspring examination, due to the higher incidence of post-implantation loss, the number of liveborn pups was considerably reduced at the highest dose (336, 330, 311 and 234 pups respectively at 0, 20, 60 and 180 mg/kg bw/d). Sex ratio, viability index, pup body weight and anogenital distance were not affected. Necropsy of pups was performed and did not reveal significant changes.

Cohort 2A : See section 10.10.2

Cohort 2B : See section 10.10.2

Cohort 3 :

One female of the lowest dose was found dead on the study day 18. During the exposure period, clinical observation and body weight examination were not affected. At necropsy, a sign. lower relative thymus weight was observed at the highest dose in males (0.152 vs 0.187 in control) (microscopic examination not performed). In this cohort, T-cell dependent antibody response (SRBC) was examined and revealed slight changes in the low and mid dose groups in females (3737, 3727, 4414 and 3599 U/ml in males, respectively at 0, 20, 60 and 180 mg/kg bw/d ; 13647, 8329, 9598 and 14555 U/ML in females, respectively at 0, 20, 60 and 180 mg/kg bw/d).

In a reproduction/developmental toxicity screening study (Anonymous 14, 2017), performed as a range finding study preceding the EOGRTS, groups of 10 male and 10 female rats were given 4,4'-sulphonyldiphenol at a concentration of 0, 30, 100 and 300 mg/kg bw/d. Animals were exposed for 10 w (for males : 6 w of pre-mating period, 2 w of mating period, and 4 w of post mating period ; and for females : 6 w of pre-mating period, 2 w of mating period, and continued through gestation and lactation periods).

No premature death occurred during the exposure period. At the highest dose, animals exhibited excessive salivation and a lower bw value (-7 % and -6 % respectively in males and females, compared to the control group).

Reproductive data were examined and revealed effects at the highest dose. Post-implantation loss was significantly higher and 2 out of 8 pregnant females had complete intrauterine litter losses. These effects resulted in a significantly lower litter size.

Table 46 : reproductive data

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

* p<0.05 ; ** : p<0.01

Necropsy revealed treatment-related effects. Uterus weight was increased in females exposed to 300 mg/kg bw/d (0.197, 0.224, 0.224 and 0.307, respectively at 0, 30, 100 and 300 mg/kg bw/d). Microscopic examination revealed also changes in these organs as well as in mammary gland in males. For more detail, see section 10.10.2

Pups were recorded and examined. At the highest dose, the total number of pups delivered was reduced (152, 127, 145 and 65 pups respectively at 0, 30, 100 and 300 mg/kg bw/d) and the mean number of pups delivered was significantly lower (15.2, 14.1, 14.5 and 10.8** respectively at 0, 30, 100 and 300 mg/kg bw/d). At PND 21, a higher body weight value was noted in male pups of the low dose group (+ 6.6 % compared to the control group). Necropsy did not reveal gross pathological findings (no further information available).

10.10.6 Comparison with the CLP criteria

Criteria for Category 1	Criteria for category 2
<p>“Known or presumed human reproductive toxicant</p> <p>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 (category 1A) or from animal data (category 1B).</p> <p>Category 1A : known human reproductive toxicant. The classification is largely based on evidence from humans</p> <p>Category 1B : presumed human reproductive toxicant. The classification 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 non-specific 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.”</p>	<p>“Suspected human reproductive toxicant</p> <p>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.</p> <p>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.”</p>

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

In the prenatal developmental toxicity study (Anonymous 19, 2014), the mean percentage of post-implantation loss was increased at the highest dose group (4.7, 3.9, 3.9 and 6.3 %, respectively at 0, 30, 100 and 300 mg/kg bw/d).

In the combined repeated dose toxicity study with reproduction/developmental toxicity screening test (Anonymous 14, 2017), the mean percentage of post-implantation loss was greatly affected by the treatment at 300 mg/kg bw/d (3.6, 5.2, 6.5 and 34.6* % at 0, 30, 100 and 300 mg/kg bw/d).

Moreover, in the parental generation of the EOGRTS (Anonymous 13, 2019), the mean number of post-implantation loss was dose-dependently increased and significant at the two highest doses (0.5, 0.8, 1.3* and 1.5** respectively at 0, 20, 60 and 180 mg/kg bw/d). This resulted in a higher percentage of post-implantation loss (3.1, 5.9, 9.4* and 10.5** % respectively at 0, 20, 60 and 180 mg/kg bw/d). As in the P generation, the cohort 1B showed a significant increased incidence of post-implantation loss (0.9, 0.8, 1.1 and 3.3** at 0, 20, 60 and 180 mg/kg bw/d, respectively). Therefore, the mean percentage of post-implantation loss was raised accordingly at the mid-dose and significantly increased at the highest dose (6.4, 5.3, 11.1 and 24.6** % at 0, 20, 60 and 180 mg/kg bw/d). The DS wants to highlight that effects were already observed at 180 mg/kg bw/d. These effects would be again more pronounced if the study would have

been dosed higher, as it is the case in the combined repeated dose toxicity study with reproduction/developmental toxicity screening test.

Post-implantation loss was increased by treatment and cannot be explained by maternal toxicity as general condition of the animals was unaffected by the treatment. Animals only exhibited excessive salivation just before or immediately after exposure to the test substance and maternal care was unaffected. Moreover, body weight examination showed variations that cannot be accounted for these effects.

According to the CLP criteria a classification as Repr. 1B for adverse effects on development is warranted based clear evidence of an adverse effect on development in the absence of toxic effect. Severe higher incidence of post-implantation loss were observed in two different studies, which cannot be related to a general toxicity.

10.10.7 Adverse effects on or via lactation

No animal studies, no human data and no other studies available

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

No information available

10.10.9 Comparison with the CLP criteria

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10.10.10 Conclusion on classification and labelling for reproductive toxicity

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

10.11 Specific target organ toxicity-single exposure

Not evaluated in this dossier

10.12 Specific target organ toxicity-repeated exposure

Not evaluated in this dossier

10.13 Aspiration hazard

Not evaluated in this dossier

11 EVALUATION OF ENVIRONMENTAL HAZARDS

Not evaluated in this dossier

12 EVALUATION OF ADDITIONAL HAZARDS

Not evaluated in this dossier

13 ADDITIONAL LABELLING

NA

14 REFERENCES

See confidential annex

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15 ANNEXES

See confidential annex

16 ABBREVIATIONS

* : p<0.05

** : p<0.01

♂ or M : male

♀ or F: female

Abs. : absolute

AGD : anogenital distance

ALP : alkaline phosphatase

ALT : alanine aminotransferase

AST : aspartate aminotransferase

BW : body weight

BWG : body weight gain

Ca : calcium

Cat. : category

Chol : cholesterol

CMC : carboxymethylcellulose

Conc. : concentration

CSA : chemical safety assessment

DIT : developmental immunotoxicity

DNT : developmental neurotoxicity

DS : dossier submitter

EOGRTS : extended one generation reproductive toxicity study

Epith. : epithelium

FBW : final body weight

GD : gestational day

GGT_C = serum- γ -glutamyltransferase

GLP : good laboratory practice

GOT : glutamic oxaloacetic transaminase

Hb : haemoglobin

HCD : historical control data

Ht : haematocrit

LD : lactation day

LDH : lactate dehydrogenase

MCHC : mean corpuscular haemoglobin concentration

MCV : mean corpuscular volume

Min. : minimum

NA : not applicable

Nb or no : number

PND : post-natal day

Pt : prothrombin time

RBC : red blood cell

Rel : relative

RET : reticulocyte

S.d : standard deviation

SD : Sprague-Dawley

Sem. ves. : seminal vesicle

Sign : significant

STOT RE : specific target organ toxicity repeated exposure

TBD : to be determined

TG : test guideline

Tot : total

Tot. chol. : total cholesterol

Tot. prot. : total protein

Trig : triglyceride

WBC : white blood cell