Committee for Risk Assessment

RAC

Annex 1

Background document

to the Opinion proposing harmonised classification and labelling at EU level of

diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide

EC Number: 278-355-8
CAS Number: 75980-60-8

CLH-O-0000007023-85-01/F

The background document is a compilation of information considered relevant by the dossier submitter or by RAC for the proposed classification. It includes the proposal of the dossier submitter and the conclusion of RAC. It is based on the official CLH report submitted to consultation. RAC has not changed the text of this CLH report but inserted text which is specifically marked as 'RAC evaluation'. Only the RAC text reflects the view of RAC.

Adopted

16 September 2021

CLH report

Proposal for Harmonised Classification and Labelling

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

International Chemical Identification: Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide

EC Number: **278-355-8**

CAS Number: **75980-60-8**

Index Number: **015-203-00-X**

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This CLH report was initially drafted by IGM Resins and submitted via the Swedish Competent Authority.

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON DIPHENYL(2,4,6-TRIMETHYLBENZOYL)PHOSPHINE OXIDE

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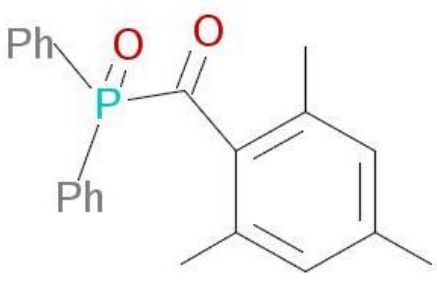
ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON DIPHENYL(2,4,6-TRIMETHYLBENZOYL)PHOSPHINE OXIDE

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)	Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide
Other names (usual name, trade name, abbreviation)	(2,4,6-Trimethylbenzoyl)diphenylphosphine oxide 2,4,6-Trimethylbenzoyl diphenyl phosphine oxide (TPO) Chivacure TPO Chivacure® TPO Darocur TPO Darocure TPO Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide Genocure TPO GENOCURE* TPO Initiator 554 Irgacure TPO JRCure TPO L-TPO Lucirin 8893X Lucirin LR 8728 Lucirin LR 8953 Lucirin TPO Lucirin TPO solid Lucirin TPO-X Omnirad TPO Phosphine oxide, diphenyl(2,4,6-trimethylbenzoyl)- (9CI) Photocure TPO Photoinitiator TPO Speedcure TPO TPO TPO-X
ISO common name (if available and appropriate)	*Not applicable*
EC number (if available and appropriate)	278-355-8
EC name (if available and appropriate)	Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide
CAS number (if available)	75980-60-8
Other identity code (if available)	*Not applicable*
Molecular formula	$C_{22}H_{21}O_2P$
Structural formula	

SMILES notation (if available)	Cc1cc(C)c(C(=O)P(=O)(c2ccccc2)c3ccccc3)c(C)c1
Molecular weight or molecular weight range	348.375
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	*Not applicable*
Description of the manufacturing process and identity of the source (for UVCB substances only)	*Not applicable*
Degree of purity (%) (if relevant for the entry in Annex VI)	*Not relevant*

1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum in multi-constituent substances)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self- classification and labelling (CLP)**
(Diphenylphosphinyl)-(2,4,6-trimethylphenyl)methanone EC: 278-355-8 CAS: 75980-60-8	≥80 - ≤100 % w/w	Repr. 2; H361f	Not Classified Skin Irrit. 2; H315 Eye Irrit. 2; H319 Skin Sens. 1; H317 Skin Sens. 1B; H317 Repr. 1B; H360 Repr. 1B; H360F Repr. 2; H361 Aquatic Acute 1; H400 Aquatic Chronic 1; H410 Aquatic Chronic 2; H411 Aquatic Chronic 3; H412 Aquatic Chronic 4; H413

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

Impurity (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**	**The impurity contributes to the classification and labelling**
Unidentified impurities not relevant for classification and labelling.	≥0 - ≤20 % w/w	Not applicable	Not applicable	Each impurity is present at <1% w/w and does not contribute towards the classification and labelling of the substance.

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**
No additives	No additives	No additives	No additives	No additives	No additives

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	015-203-00-X	diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide	278-355-8	75980-60-8	Repr. 2	H361f	GHS08 Wng	H361f			
Dossier submitters proposal	015-203-00-X	diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide	278-355-8	75980-60-8	Add Skin Sens. 1B Modify Repr. 1B	Add H317 Modify H360Fd	Add GHS07 GHS08 Dgr	Add H317 Modify H360Fd			
Resulting Annex VI entry if agreed by RAC and COM	015-203-00-X	diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide	278-355-8	75980-60-8	Skin Sens. 1B Repr. 1B	H317 H360Fd	GHS07 GHS08 Dgr	H317 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 classes not assessed in this dossier	No
Flammable gases (including chemically unstable gases)	Hazard classes not assessed in this dossier	No
Oxidising gases	Hazard classes not assessed in this dossier	No
Gases under pressure	Hazard classes not assessed in this dossier	No
Flammable liquids	Hazard classes not assessed in this dossier	No
Flammable solids	Hazard classes not assessed in this dossier	No
Self-reactive substances	Hazard classes not assessed in this dossier	No
Pyrophoric liquids	Hazard classes not assessed in this dossier	No
Pyrophoric solids	Hazard classes not assessed in this dossier	No
Self-heating substances	Hazard classes not assessed in this dossier	No
Substances which in contact with water emit flammable gases	Hazard classes not assessed in this dossier	No
Oxidising liquids	Hazard classes not assessed in this dossier	No
Oxidising solids	Hazard classes not assessed in this dossier	No
Organic peroxides	Hazard classes not assessed in this dossier	No
Corrosive to metals	Hazard classes not assessed in this dossier	No
Acute toxicity via oral route	Hazard classes not assessed in this dossier	No
Acute toxicity via dermal route	Hazard classes not assessed in this dossier	No
Acute toxicity via inhalation route	Hazard classes not assessed in this dossier	No
Skin corrosion/irritation	Hazard classes not assessed in this dossier	No
Serious eye damage/eye irritation	Hazard classes not assessed in this dossier	No
Respiratory sensitisation	Hazard classes not assessed in this dossier	No
Skin sensitisation	Harmonised classification proposed	**Yes**
Germ cell mutagenicity	Hazard classes not assessed in this dossier	No
Carcinogenicity	Hazard classes not assessed in this dossier	No
Reproductive toxicity	Harmonised classification proposed	**Yes**
Specific target organ toxicity-single exposure	Hazard classes not assessed in this dossier	No
Specific target organ toxicity-repeated exposure	Hazard classes not assessed in this dossier	No
Aspiration hazard	Hazard classes not assessed in this dossier	No
Hazardous to the aquatic environment	Hazard classes not assessed in this dossier	No
Hazardous to the ozone layer	Hazard classes not assessed in this dossier	No

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

The current harmonised classification and labelling entry for the substance Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide (index number 015-203-00-X) was inserted in ATP03 to CLP Annex VI based upon the consultation conducted in 2010 (dossier submitted by Germany). In the consultation, little information on reproductive toxicology was available and the reproductive toxicity potential of the substance was assessed based upon a 28-day and 90-day repeated dose toxicity study. Both the 28- and 90-day studies showed clear evidence for atrophy of the testes as an indication of reduced fertility of the test animals. Reproductive effects including effects on fertility were not investigated in the studies available at the time of the consultation in 2010.

Since then, an OECD TG 421 study has been performed demonstrating adverse effects on male reproductive organs and impairment of both mating and fertility.

RAC general comment
Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide (TPO) (index number 015-203-00-X) was placed on Annex VI of CLP with a classification as Repr.2 H361f in ATP03. Limited information on reproductive toxicity was available and the assessment was based upon three studies: an oral 28-day repeated dose toxicity study, an oral 90-day repeated dose toxicity study, and a second (non-GLP compliant) oral 28-day and 90-day repeated dose toxicity study. Since then, one OECD TG 421 study two OECD TG 414, as well as an OECD TG 429 study have been performed and are included in the current assessment.

4 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:

- Change in existing entry due to new data for reproductive toxicity.
- Differences in self-classification for skin sensitisation.

Further detail on need of action at Community level:

According to Article 36(3) of CLP Regulation for a substance that fulfils the criteria for other hazard classes or differentiations than those of CMR or respiratory sensitization (Category 1) and the substance is not an active substance regulated under the Plant Protection Product Directive (PPPD) and Biocidal Product Directive (BPD), a harmonised classification and labelling proposal can be submitted if a justification is provided demonstrating the need for such action at community level.

Reproductive toxicity:

It is proposed that diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide is reclassified as Repr. 1B, H360Fd based on new data generated since the previous decision on harmonised classification.

Skin sensitisation:

A classification in Skin Sens. 1B will lead to correct labelling requirements for substances and for mixtures containing the substance and is currently regarded as the most important risk management measure for skin sensitisers. In the C&L Inventory, the majority of notifiers (> 2500) has not notified diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide as a skin sensitiser in Category 1 or 1B.

5 IDENTIFIED USES

The substance Omnirad TPO is a highly efficient, low yellowing, Type I photoinitiator used to initiate radical polymerization of unsaturated oligomers e.g., acrylates, after exposure to UV light. It can be used in combination with mono- or multi-functional monomers as reactive diluents.

The substance is manufactured both inside and outside of the EU and is formulated into mixtures both inside and outside the EU. Mixtures are used within the EU to produce articles, which are used both inside and outside the EU.

Formulation of mixtures takes place in both industrial and professional settings with a variety of activities and risk control methods and efficiencies. Mixed products are supplied in both large (pre-blends and bulk coating products) and smaller (inks, toners, and coatings) packages ranging from ca. 0.2L - 200L.

Mixtures are used across a variety of industry and professional sectors, including Graphic Arts, Wood Coatings, Plastic Coatings, Metal Coatings.

6 DATA SOURCES

See annex I.

7 PHYSICOCHEMICAL PROPERTIES

Table 7: Summary of physicochemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3 kPa	Solid – yellow powder	ECHA Dissemination site, 2020	Measured
Melting/freezing point	93 °C	ECHA Dissemination site, 2020	Measured
Boiling point	Substance decomposes before boiling above 200 °C	ECHA Dissemination site, 2020	Data waiver
Relative density	1.218 at 20 °C	ECHA Dissemination site, 2020	Measured
Vapour pressure	3.045E-6 Pa at 25 °C	ECHA Dissemination site, 2020	Measured
Surface tension	Data waiver	Data waiver	Data waiver
Water solubility	3.4 mg/L at 20 °C	ECHA Dissemination site, 2020	Measured
Partition coefficient n-octanol/water	Log Kow 3.1 at 23 °C	ECHA Dissemination site, 2020	Measured
Flash point	Data waiver	Data waiver	Data waiver
Flammability	Data waiver	Data waiver	Data waiver
Explosive properties	Data waiver	Data waiver	Data waiver

ANNEX 1 - BACKGROUND DOCUMENT TO RAC OPINION ON DIPHENYL(2,4,6-TRIMETHYLBENZOYL)PHOSPHINE OXIDE

Property	**Value**	**Reference**	**Comment (e.g. measured or estimated)**
Self-ignition temperature	No self-heating detected up to 400 °C	ECHA Dissemination site, 2020	Measured
Oxidising properties	Data waiver	Data waiver	Data waiver
Granulometry	40.2 % <100 micron 0.2 % <10 micron 0 % <4 micron	ECHA Dissemination site, 2020	Measured
Stability in organic solvents and identity of relevant degradation products	Data waiver	Data waiver	Data waiver
Dissociation constant	Data waiver	Data waiver	Data waiver
Viscosity	Data waiver	Data waiver	Data waiver

8 EVALUATION OF PHYSICAL HAZARDS

Not evaluated in this CLH-proposal.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

9.1 Short summary and overall relevance of the provided toxicokinetic information on the proposed classification(s)

There are no studies available for the determination of toxicokinetics or dermal absorption. The following information is presented to assist with evaluating the level of concern posed by the substance.

Diphenyl(2,4,6 -trimethylbenzoyl)phosphine oxide is a powder with a molecular weight of 348 g/mol and a very low vapour pressure of 3x10e6 Pa at 25 °C. In agreement with its logPow of 3.1, only 3 mg can be dissolved in one litre of water. Due to its low vapour pressure, exposure to vapor is unlikely. The combination of a molecular weight below 500 g/mol and moderate lipophilicity (logPoW between 1 and 4) favour oral as well as dermal uptake. Based on effects observed in oral *in vivo* toxicity studies (kidney, liver and reproductive organs), oral uptake and systemic availability is demonstrated.

10 EVALUATION OF HEALTH HAZARDS

Acute toxicity

10.1 Acute toxicity - oral route

Not evaluated in this CLH-proposal.

10.2 Acute toxicity - dermal route

Not evaluated in this CLH-proposal.

10.3 Acute toxicity - inhalation route

Not evaluated in this CLH-proposal.

10.4 Skin corrosion/irritation

Not evaluated in this CLH-proposal.

10.5 Serious eye damage/eye irritation

Not evaluated in this CLH-proposal.

10.6 Respiratory sensitisation

Not evaluated in this CLH-proposal.

10.7 Skin sensitisation

Table 8: Summary table of animal studies on skin sensitisation

<table>
<tr><th>Method, guideline, deviations if any</th><th>Species, strain, sex, no/group</th><th>Test substance, dose levels, duration of exposure</th><th>Results</th><th>Reference</th></tr>
<tr>
<td>OECD Guideline 429 (Skin Sensitisation: Local Lymph Node Assay, LLNA).

EU Method B.42 (Skin Sensitisation: Local Lymph Node Assay).</td>
<td>Mouse, CBA,

5 females per group.

Age at study initiation: 9-10 weeks during pre-test, and 8-9 weeks during main experiment.</td>
<td>(Diphenylphosphinyl)-(2,4,6-trimethylphenyl) methanone.

Dose levels: 10%, 25%, 50% (w/w) verified analytically.

Exposure: Applied once a day for 3 days.

Vehicle: Acetone/olive oil (4:1 v/v).

Positive control substance: hexyl cinnamic aldehyde (CAS No 101-86-0).</td>
<td>
<table>
<tr><td>Parameter</td><td>Test group</td><td>Value (SI)</td></tr>
<tr><td>SI</td><td>Vehicle</td><td>1.00</td></tr>
<tr><td>SI</td><td>10%</td><td>2.22</td></tr>
<tr><td>SI</td><td>25%</td><td>2.96</td></tr>
<tr><td>SI</td><td>50%</td><td>3.45</td></tr>
<tr><td>EC3</td><td></td><td>27.0%</td></tr>
</table>
LLNA endpoints – stimulation index (SI); EC3; disintegrations per minute (DPM).

No significant increase in ear weights, as well as no signs of local or systemic toxicity were observed. The test substance was found to be a sensitizer, the EC3 value was calculated to be 27%.

A statistically significant increase in DPM value and also in lymph node weight was observed in all dose groups in comparison to the vehicle control group ($p<0.05$). A statistically significant and biologically relevant increase in lymph node cell count was observed in the mid (25%) and high (50%) dose group in comparison to the vehicle control group ($p<0.05$). Furthermore, the cut-off-value for a positive response regarding the lymph node cell count index of 1.55 reported for BALB/c mice was exceeded in the mid and high dose group (indices of 1.91 and 1.83, respectively).

All treated animals survived the scheduled study period and no signs of systemic toxicity or local skin irritation were observed.
</td>
<td>Study report, 2012</td>
</tr>
</table>

Table 9: Summary table of human data on skin sensitisation

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No data	No data	No data	No data	No data

Table 10: Summary table of other studies relevant for skin sensitisation

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No data	No data	No data	No data	No data

10.7.1 Short summary and overall relevance of the provided information on skin sensitisation

Diphenyl(2,4,6-trimethylbenzoyl)phosphine (TPO) was assessed for its skin sensitising potential using the Local Lymph Node Assay (LLNA) in mice . The study was conducted according to the OECD guideline 429 and the EU method B.42 in a GLP compliant laboratory and is considered to be reliable without restriction.

Stimulation Indices (S.I.) of 2.22, 2.96, and 3.46 were determined at concentrations of 10, 25, and 50% (w/w) TPO in acetone:olive oil (4+1 v/v), respectively. A clear dose response was observed. Based on the S.I.'s obtained with 25 and 50% TPO concentration, an EC3 value of 27.0% (w/w) was calculated. No signs of systemic toxicity or local skin irritation were observed in the study.

There is no information available on skin sensitisation in humans.

10.7.2 Comparison with the CLP criteria

The CLP Regulation allows classification of skin sensitizers in one hazard category, Category 1, which comprises two sub-categories, 1A and 1B. For Category 1, when the LLNA is used, a SI of ≥ 3 is considered positive. This criterion is fulfilled for TPO which has a SI of 3 at a TPO concentration of 27% (EC3 value). Classification into sub-categories should be performed if data is sufficient (CLP Annex I 3.4.2.2.1.1). Criteria for sub-categorisation into 1A and 1B includes data with the below indicated values, according to the CLP Regulation (Table 3.4.3 and 3.4.4).

Criteria for sub-category classification of skin sensitizers.

Sub-category	Assay	Response
1A	LLNA	EC 3 ≤ 2%
1B	LLNA	EC 3 > 2%

TPO has an EC3 value of 27% and hence fulfils the criteria for sub-categorisation in 1B (EC 3 > 2%).

10.7.3 Conclusion on classification and labelling for skin sensitisation

Classification of TPO as Skin Sens. 1B, H317 is proposed.

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

The DS included one Local Lymph Node Assay (LLNA) performed according to OECD TG 429 and GLP in mice. Stimulation Indices (S.I.) of 2.22, 2.96, and 3.46 were determined at concentrations of 10, 25, and 50% (w/w) TPO in acetone:olive oil (4+1 v/v), and an EC3 value of 27.0% (w/w) was calculated. The DS concluded that a classification as Skin Sens 1B, H317 was justified.

Comments received during consultation

Three Member States (MS) commented on and supported the proposed classification as Skin Sens. 1B, H317.

Assessment and comparison with the classification criteria

One LLNA according to OECD TG 429 and GLP was included by the DS for the assessment of skin sensitising properties of TPO. The DS considered the study to be reliable without restriction. In the study, 5 female CBA mice per dose group were exposed once daily for three days to TPO in acetone:olive oil (4+1 v/v). Hexyl cinnamic aldehyde (CAS No 101-86-0) was used as positive control. No significant increase in ear weights, as well as no signs of local or systemic toxicity were observed. All treated animals survived the scheduled study period (Study report, 2012). Stimulation Indices (S.I.) of 2.22, 2.96, and 3.46 were determined at concentrations of 10, 25, and 50% (w/w) TPO in acetone:olive oil (4+1 v/v), respectively. Based on the S.I.'s obtained with TPO at a concentration of 25 and 50%, an EC3 value of 27.0% (w/w) was calculated.

There is no information available on skin sensitisation in humans.

The CLP Regulation allows classification of skin sensitisers in one hazard category, Category 1, which comprises of two sub-categories, 1A and 1B. The classification can be based on data from LLNA studies, where a category 1A is justified if the EC3 value is ≤ 2 while a category 1B is justified if the EC3 value is ≥2.

Overall, RAC is of the opinion that a classification of TPO as **Skin Sens. 1B, H317** is justified based on the EC3 value of 27%.

10.8 Germ cell mutagenicity

Not evaluated in this CLH-proposal.

10.9 Carcinogenicity

Not evaluated in this CLH-proposal.

10.10 Reproductive toxicity

10.10.1 Adverse effects on sexual function and fertility

Table 11: Summary table of animal studies on adverse effects on sexual function and fertility

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, dose levels, duration of exposure	Results	Reference
OECD Guideline 421 (Reproduction /Developmental Toxicity Screening Test) – no deviations. EPA OPPTS 870.3550, Reproduction/ Developmental Toxicity Screening Test - no deviations. The experimental start and end date: 16 May 2018 - 20 Sep 2018.	Rat, Wistar Han, 10 males and 10 females per group.	Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide. Purity: 99.32%. Dose levels: 0, 60, 200 and 600 mg/kg bw/day. Exposure: Oral, gavage, once daily. Males treated for a min. of 10 weeks prior to mating (covering at least one spermatogenic cycle) and mating (in total 13 weeks or 85-92 days). Females treated for 10 weeks prior to mating (covering at least two estrous cycles), the variable time to conception, the duration of pregnancy and at least 20 days after delivery (in total 18 weeks or 113-127 days). Vehicle: Water, 1% Aqueous carboxymethyl cellulose.	**Mortality** Two preterm decedents during premating period; One female (600 mg/kg) was sacrificed in extremis due to moderate lethargy, flat/hunched posture, muscle twitching, piloerection, slight chromodacryorrhoea, slight ptosis, red snout and slight bodyweight loss (2%), and one female (control group) was found dead before dosing on Day 43. One female (200 mg/kg) was euthanized on lactation Day 4, due to litter loss (delivered only one pup). **Clinical signs** (only observed at 600 mg/kg bw) Except for the female sacrificed in extremis (abovementioned), one female had transient signs of muscle twitching, hunched posture and piloerection, and two more females had piloerection. All males showed transient signs of abnormal calm/lethargic behaviour and one male had breathing rales. **Food consumption** No changes in absolute or relative food consumption in females or males of all groups. **Body weight** A dose-response related lower body weight and body weight gain were observed in males at 200 and at 600 mg/kg during premating and mating period. The body weight and body weight gain were significantly reduced from Week 7 resp. from Week 9 onwards (p <0.05). Body weight was 9% (at necropsy) and 13% (at end of treatment) lower in males at 200	Study report, 2019

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, dose levels, duration of exposure	Results	Reference
			resp. at 600 mg/kg than in controls. **Functional tests** (end of premating period) Performed on five males and five females per group. An overall decrease in results was observed but remained within the available historical control range for the strain and age. **Mating Index** Mating indices were 67% (6/9 females) at 600 mg/kg and 100% for all other groups. Mating index at 600 mg/kg was below the 5th percentile of the historical control range (mean=99%, P5-P95=90-100%, N=98). **Oestrous cycle** Extended dioestrus cycle was observed in 3/9 females at 600 mg/kg (referring to those females that were not mated) and in one female at 60 mg/kg. **Precoital time** One female at 60 mg/kg (with extended di-oestrus cycle) had a precoital time of 14 days. Two other females (at 0 and 60 mg/kg) had a precoital time of 5-6 days. **Number of implantation sites** All mated females at 600 mg/kg (6/9) and one female at 60 mg/kg (with regular oestrous cycle) presented with 0 implantation sites (and 0 corpora lutea). **Fertility index** Fertility indices were 0%, 100%, 90% and 100% at 600, 200, 60 and 0 mg/kg, respectively. **Gross Pathology** At 600 mg/kg bw, macroscopic findings in males at necropsy showed flaccid testes (8/10) as well as reduced size of testis (10/10 animals) and of epididymides (9/10 animals). The findings were significantly (p <0.01) different from controls.	

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, dose levels, duration of exposure	Results	Reference
			Organ weights *Testes* At 600 mg/kg bw, mean weight of testes was significantly (p <0.01) lower than in controls (- 52% for absolute weight, and - 45% for relative to body weight). *Epididymides* At 600 mg/kg bw, mean weight of epididymides were significantly (p <0.01) lower than in controls (- 43% for absolute weight and - 34% for relative to body weight). At 200 mg/kg, males had a significantly (p <0.05) lower mean absolute epididymides weight (- 11%) and a lower relative epididymides weight (- 1%) than controls. *Seminal vesicles* At 600 mg/kg, mean absolute weight of seminal vesicles was 8% higher than in controls, reaching statistical significance for relative weight (24%, p < 0.01). The effect was not dose-response related. *Thyroid* At 600 mg/kg, mean absolute weight of thyroid was higher than in controls (0.020 vs 0.019 grams), reaching statistical significance only for relative weight (0.006 vs 0.005, p <0.05). Also, a higher relative thyroid weight was observed in females, but non-significant (0.007 vs 0.006). The absolute thyroid weight in females was however lower than in controls. The effects observed in males and females were not dose-response related. **Histopathology** *Testes* Tubular atrophy at massive degree in all males at 600 mg/kg. This correlated with macroscopic findings of flaccid and/or reduced in size of testes as well as decreased testis weight. Atypical residual bodies at slight to moderate degree in all males at 200 mg/kg. Multinucleated giant cells at moderate degree in one male at 200 mg/kg and one male at 600 mg/kg.	

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, dose levels, duration of exposure	Results	Reference
			Degeneration and depletion of germ cell at moderate degree in one male (200 mg/kg). *Epididymides* Cell debris present at moderate degree in one male (200 mg/kg) and at minimal to moderate degree in 8/10 males (600 mg/kg). Reduced sperm at slight degree in one male (200 mg/kg) and at massive degree in all males (600 mg/kg). This correlated with macroscopic findings of reduced size of epididymides and decreased epididymides weight. *Thyroid gland* Hypertrophy follicular cell at slight degree in 4/10 males (200 mg/kg) and 3/10 males (600 mg/kg) as well as in 2/10 females (600 mg/kg). Colloid alteration at slight degree in 4/10 males (600 mg/kg) and in 1/10 females (600 mg/kg).	
Equivalent or similar to OECD Guideline 408 (Repeated Dose 90-Day Oral Toxicity in Rodents) based on EPA-TSCA Guideline "Functional Observational Battery" & EPA-TSCA Guideline " Neuropathology" (Federal Register Vol. 50,	Rat, Wistar, 10 males and 10 females per treatment group. Age at study initiation: ~ 5 weeks.	Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide. Purity: 94.8%. Dose levels: 0, 100, 300 and 1000 mg/kg bw/day. Exposure: Oral gavage, once daily on workdays (5 days/ week) for 90 days. Vehicle: CMC (carboxymethyl cellulose) 0.5% in water.	**Mortalities** (only observed at 1000 mg/kg) Two females died on Day 44 and 48 during the exposure period. **Clinical signs** (only observed at 1000 mg/kg) Females showed a reduced general state of health. Lesions on the hairless skin of the extremities as well as reddening and scale formation on the ears were reported for females and males. **Body weight** At 1000 mg/kg, body weight and body weight gain were reduced in females (8 % resp. 16 %) and in males (23 % resp. 38 %). At 300 mg/kg, body weight and body weight gain reduction were only observed in males (10 % resp. 16 %). **Food consumption** An increase in food consumption was reported for females at 1000 mg/kg.	Study report, 1991

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, dose levels, duration of exposure	Results	Reference
No. 188). GLP compliant.			**Gross pathology at necropsy** In males (300 and 1000 mg/kg), the testes were reduced in size, which was palpable from week 6 and onwards. At 100 mg/kg, one male exhibited moderately reduced spermiogenesis. All males of this dose group showed a minimal to moderate vacuole degeneration of spermatogonia in some seminiferous tubules. **Organ weights** At 300 and 1000 mg/kg, the absolute and relative testes weights were decreased, on average by about 50% in all males. **Histopathology** At 300 and 1000 mg/kg, all males had moderate to marked degree of diffuse atrophy of the testicular parenchyma and a slight to moderate degree of interstitial oedema.	
Equivalent or similar to OECD Guideline 408 (Repeated Dose 28 and 90-Day Oral Toxicity in Rodents). Not GLP compliant.	Rat, Wistar Han, 3 males in the 28-day study and 10 males in the 90-day study Age at study initiation: 41-43 days in the 28-day study and 34 days in the 90-day study.	Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide. Purity: 99.3%. Dose levels: 0 and 1000 mg/kg bw/day. Exposure: Oral, gavage, once daily for 28 days and 90 days. Vehicle: CMC (carboxymethyl cellulose) 0.5% in water.	**Mortality** No mortality reported. **Clinical signs** No adverse effects reported. **Body weight** Body weight reduction of 10% in the 90-day study. No effect was observed in the 28-day study. **Gross pathology at necropsy** *Testes* In 8/10 males, testes were reduced in size and loss of turgor was observed in the 90-day study, but not in the 28-day study. *Epididymides* In 8/10 males, epididymides was reduced in size in the 90-day study, but not in the 28-	Study report, 2001

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, dose levels, duration of exposure	Results	Reference
			day study. **Organ weights** Mean testes weights were significantly lower in the 90-day study (mean absolute weight 2.1 grams and mean relative weight 0.718) compared to the control group (mean absolute weight 3.286 grams and mean relative weight 0.996). No effect was observed in the 28-day study. **Histopathology** In the 90-day study, all testes showed slight to severe degree of diffuse atrophy of seminiferous tubules and testicular atrophy. The 8/10 epididymides with reduced organ size correlated with (up to) severe degree of oligozoospermia (azoospermia). Four males had oedema and Leydig cell hyperplasia of minimal to slight degree. No histomorphological changes observed in the 28-day study.	
Japanese Ministry of Health and Welfare (M .H .W .) guidelines 1986 for a Repeated Dose 28-Day Oral Toxicity study. GLP compliant.	Rat, Sprague-Dawley, 5 males and 5 females per group. Satellite groups: 5 males and 5 females of the control and the high dose group. 14-days of treatment-	Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide Purity: 99%. Dose levels: 0, 50, 250 and 750 mg/kg bw/day. Exposure: Oral, gavage, once daily for 28 days. Satellite group animals were examined at the end of the treatment-free period (i.e. 14 days after 28-day treatment). Vehicle: Arachis oil.	**Mortality** One female from the satellite high dose group was found dead on Day 4 and one female from the satellite control group died on Day 42 (post-treatment period). **Clinical signs** At 750 mg/kg, increased salivation, red/brown staining around the snout and mouth, wet fur, red/brown staining of the fur, hair loss, piloerection, hunched posture, lethargy, ptosis, diuresis, diarrhoea and abdominal distension, and single incidence of vocalisation were observed from Day 3 and onwards. Satellite animals recovered immediately following cessation of dosing and appeared normal throughout the treatment-free period. At 250 mg/kg, the same clinical signs as the animals at 750 mg/kg, but with less severity and without diarrhoea, abdominal distension, and vocalisation, was observed from Day 4 and onwards. **Body weight**	Study report, 1989

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, dose levels, duration of exposure	Results	Reference
	free period after end of treatment. Age at study initiation: 6-7 weeks old.		At the end of treatment, body weight was reduced in animals at 250 mg/kg (mean -5%) and at 750 mg/kg (mean -14%) compared to controls. Females of the satellite group were not affected. Weight gains quickly recovered in satellite high dose males during the treatment-free period. **Food consumption** No effects on food consumption in males or females, except for a marked reduction in food efficiency during the last week of treatment in the 250 and the 750 mg/kg groups, which was related to the lower body weight (see above). Food efficiency turned back to normal in the 750 mg/kg satellite group following cessation of treatment. **Gross pathology at necropsy** At 750 mg/kg, the males had abnormally small testes. Three females displayed ventral fur loss and brown staining of the anogenital area. In the satellite group, one male had small testes. **Organ weights** At 750 mg/kg, males displayed a reduction in testes weight (mean absolute weight 3.09 grams and mean relative weight 0.91) that was identified microscopically as testicular atrophy, compared to controls (mean absolute weight 3.39 grams and mean relative weight 1.04). The mean relative weight in the satellite group was 0.85. **Histopathology** *Testes* Testicular atrophy, frequently bilateral, was seen in all males at 750 mg/kg. Testicular atrophy was also present amongst the males in the satellite group (750 mg/kg), although the incidence was reduced (3/5).	

Table 12: Summary table of human data on adverse effects on sexual function and fertility

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
No data	No data	No data	No data	No data

Table 13: Summary table of other studies relevant for toxicity on sexual function and fertility

Type of study/data	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
No data	No data	No data	No data	No data

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

The current harmonised classification of Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide as Repr. 2 (H361f), adopted by RAC in 2010, is based on three studies; an oral 28-day repeated dose toxicity study, an oral 90-day repeated dose toxicity study, and a second (non-GLP compliant) oral 28-day and 90-day repeated dose toxicity study.
RAC concluded in their opinion that the testes are a target organ for diphenyl (2,4,6-trimethylbenzoyl)phosphine oxide in rat (and could potentially lead to reduced male fertility) and that the adverse effects occur in the absence of significant generalised toxicity. However, due to the limitations of the studies, the evidence was not sufficiently convincing to place the substance in Category 1B.
RAC also commented on available data missing for female fertility and multi-generation studies investigating the potential effects on fertility.

In 2018, an oral reproduction/developmental toxicity screening test (OECD 421) was performed as a range-finder test for an extended one-generation reproductive toxicity study (OECD 443) that was requested in a dossier evaluation decision.

In the **28-day oral repeated dose toxicity study** (**Study report, 1989**), the test substance was administered to five Sprague-Dawley rats per sex and group at dose levels of 0, 50, 250, or 750 mg/kg bw/day. The control group received the vehicle alone. Two satellite groups, each of five rats per sex were treated with the high dose (750 mg/kg bw/day) or the vehicle alone throughout the 28-day study period and then maintained without treatment for additionally fourteen days.

Decreased testes weight and size, microscopically identified as testicular atrophy, was observed in all high dose males. Grading indicated increased severity of testicular atrophy at the high dose. Although one animal from each of the remaining treatment group also had a minimal degree of testicular atrophy, the study author considered it to be spontaneous in origin and unrelated to treatment at these dose levels. Testicular atrophy was also present amongst males in the satellite group (750 mg/kg), although the incidence was reduced (3/5). Clinical signs were reported at 250 mg/kg and 750 mg/kg with increasing severity in the high dose group. Body weight was reduced at 250 mg/kg (5%) and at 750 mg/kg (14%) as compared to the control group. Weight gains quickly recovered during the treatment-free period as observed in the males of the satellite high dose group.

In the **90-day oral repeated dose toxicity study** (**Study report, 1991**), intended to look for neuropathological effects of the test substance, confirmed the treatment-related effects on testes observed in the 28-day repeated dose toxicity study. The test substance was administered to ten Wistar rats per sex and group at dose levels of 0, 100, 300, or 1000 mg/kg bw/day. The control group received the vehicle alone.

A decrease in absolute and relative testes weight (on average by about 50%) as well as diffuse atrophy of the testicular parenchyma and interstitial oedema was observed at 300 mg/kg and 1000 mg/kg. In the 100 mg/kg dose group, one animal exhibited moderately reduced spermiogenesis. All animals of the 100 mg/kg dose group showed a minimal to moderate vacuole degeneration of spermatogonia in some seminiferous tubules. These lesions and the focal atrophy findings were also seen in the control group up to the same grading and are not considered to be substance related by the study author. There were no mortalities or severe clinical signs reported in males in any dose group. Body weight and body weight gain were reduced in males from 300 mg/kg. At 300 mg/kg, body weights were 10 % lower and at 1000 mg/kg body weights were 23% lower compared to the control group.

In the second **28-day oral repeated dose toxicity study** (**Study report 2001**), no testicular effects were noted in the three male Wistar rats dosed at 1000 mg/kg bw/day compared to the control group receiving the vehicle alone. No mortalities or clinical signs were reported.

In the second **90-day oral repeated dose toxicity study** (**Study report, 2001**), the ten Wistar rats, dosed at 1000 mg/kg bw/day, had decreased absolute and relative mean weight of testes, reduced testes size, loss of turgor, and slight to severe diffuse atrophy (mostly bilateral) of the seminiferous tubules in the testes. In four cases, oedemas as well as a minimal to slight hyperplasia of the Leydig cells were also seen. The epididymis was reduced in size and histopathology revealed oligo- to azoospermia (i.e. reduction in or absence of mature sperms). No mortalities or clinical signs were reported. Body weight was reduced by 10% compared to the control group.

In the **reproduction/developmental toxicity screening test OECD 421** (**Study report, 2019**), the test substance was administered to ten Wistar rats per sex and group at dose levels of 0, 60, 200, and 600 mg/kg bw/day to evaluate the potential to affect male and female reproductive performance such as gonadal function, mating behaviour, conception, parturition and early postnatal development. An elongated pre-mating period of 10 weeks was included, to cover at least one complete spermatogenic cycle and at least two complete oestrous cycles. The control group received the vehicle alone. The dose levels were selected based on the results of the 90-day repeated dose toxicity study (study report, 1991).

At 600 mg/kg, one female was sacrificed in extremis during the premating period for animal welfare reasons as the female presented with moderate lethargy, flat/hunched posture, muscle twitching, piloerection, slight chromodacryorrhoea, slight ptosis, and red snout. Slight (2%) body weight loss was noted for this female over Weeks 7-8 of the premating period, followed by recovery in Week 9. During the macroscopic examination at necropsy, accentuated lobular pattern of liver and reduced size of the spleen were noted. Although no definite cause of moribundity could be established from the microscopic examination of the selected tissues, the study author states that a relationship to treatment could not be excluded as comparable clinical signs were noted for a surviving high dose female as well. The other preterm decedent (one control female during the premating period) was regarded to be unrelated to treatment with the test item. In addition, one female at 200 mg/kg was euthanized on PND4 as she had a total litter loss during the lactation period.

According to the study author, treatment-related clinical signs were noted in males and females at 600 mg/kg at the end of the premating period, including transient signs of abnormal behaviour and/or posture. During 7 days at the end of Week 8 of treatment, all males at 600 mg/kg were noted less reactive (slightly calm/lethargic). In addition, one female at 600 mg/kg was observed on three different occasions during Week 10-11 of treatment with transient muscle twitching in combination with hunched posture and/or piloerection on 1 or 2 occasions. These clinical signs were short in duration (lasting for only a few minutes), followed by complete recovery. As similar clinical signs were also noted in the high dose female sacrificed in extremis, these observations were regarded as related to treatment. In addition, piloerection was also noted in this female and two other females treated at 600 mg/kg for 2 to 3 consecutive days at the end of Week 13 or 16 of treatment.

Test item-related effects on body weight and body weight gain were observed in males at 200 and 600 mg/kg during both the premating and mating period. High dose males presented with a slightly reduced mean body weight gain from start of treatment onwards (reaching statistical significance on Day 8 and from Day 57 onwards), resulting in a 13% lower mean body weight at the end of treatment when compared with control values. The reduced mean body weight observed in males at the dose level of 200 mg/kg at the end of the treatment period was considered non-adverse, based on the slight magnitude of the change (less than 10%) and as no other relevant clinical signs were noted at this dose level. The lower body weight gain and absolute food consumption noted in females at 600 mg/kg during the gestation period were considered to be related to the non-

pregnancy status of all the females at this high dose level, and as such not to reflect a systemic toxic effect of the test item.

A dose-dependent decrease of total movements and ambulations was noted in females, but changes did not reach statistical significance and all mean values remained within the available range of historical control range. Therefore, no toxicological relevance was attached to this finding. Also in males, a slight decrease in motor activity (non-significant) was observed at 600 mg/kg but mean values remained within the normal range. Although, this decrease was considered not toxicologically relevant, a relationship with treatment could not be discarded based on the clinical signs observed at this dose level.

Macroscopic observations at necropsy revealed test item-related alterations in the reproductive organs of males at 600 mg/kg: macroscopic findings were present in the testes as flaccid (8/10 animals) and reduced in size (10/10 animals) and in the epididymides as reduced in size (9/10 animals). A test item-related decrease in organ weights of testes and epididymides (absolute and relative to body weight) were noted in males at 600 mg/kg. Differences vs control in organ:body weight ratios were 45% and 34% for testes and epididymis, respectively. Adverse test item-related microscopic findings were noted in the testes and epididymides in males starting at 200 mg/kg. Relationships were observed between gross necropsy, organ weight, and histopathology observations. The massive tubular atrophy observed in testes at 600 mg/kg was considered adverse. In addition, the atypical residual bodies in males at 200 mg/kg and the single male with degeneration/depletion of germ cells at 200 mg/kg were also considered adverse. In the epididymides; the massive reduced sperm at 600 mg/kg and the slight reduced sperm at 200 mg/kg with minimal to moderate cell debris were considered adverse.

Non-adverse test item-related microscopic findings were noted in the thyroid gland in males at 200 and 600 mg/kg and in females at 600 mg/kg. The minimal increase in hypertrophy of the follicular epithelium of the thyroid glands and the colloid alteration seen in males starting at 200 mg/kg and in females at 600 mg/kg was considered non-adverse at current severities and in absence of any other adverse pathologic findings. No treatment-related changes were noted in any of the remaining parameters investigated in this study (i.e. food consumption and male T4 thyroid hormone).

Mating index was lower at 600 mg/kg (67%, 6/9 females) when compared with concurrent control (100%) and mean historical control value (99%). During the mating period, extended di-oestrus was observed in the 3/9 high dose females for which mating could not be confirmed, even though they had been cohoused for another 7 days with a male of the same group for which mating was already confirmed. Although an extended di-oestrus occasionally occurs at low incidence in untreated controls, a relation to treatment with the test item could not be excluded.

At 600 mg/kg, the **fertility index** was 0%. There were 9/9 couples treated at 600 mg/kg, compared to 2/10 at 200 mg/kg and 1/10 at 60 mg/kg, that failed to deliver pups. All the males treated at 600 mg/kg showed massive tubular atrophy in the testes and reduced luminal sperm with luminal cell debris in the epididymides which accounted for the lack of offspring. The lack of offspring for one couple treated at 200 mg/kg (female with only implantations) could be explained by the moderate depletion and degeneration of sperm cells with multinucleated giant cells in the testes and moderate cell debris and slight reduced sperm in the epididymides in the male. The rest of the males treated at 200 mg/kg all showed atypical residual bodies, which apparently did not affect their fertility.

10.10.3 Comparison with the CLP criteria

Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide fulfils the criteria of Category 1B as it exhibits adverse effects on the testes and epididymides, in absence of marked general toxicity, which lead to reduction in fertility. Reduced weight of the testes and histopathological effects was also noted in the 28-day (study report, 1989) and 90-day (Study report, 1991) repeated dose toxicity studies.

This is considered as clear evidence and there is no indication that raises doubt on the relevance of this effect for humans.

Classification in Repr. 1A is not appropriate as it should be based on human data and no human data of Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide is available.

Classification in Repr. 2 is not appropriate as the evidence for adverse effects on sexual function and fertility from existing experimental data on Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide are considered as clear evidence and not as some evidence.

10.10.4 Adverse effects on development

Table 514: Summary table of animal studies on adverse effects on development

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, dose levels, duration of exposure	Results	Reference
OECD Guideline 414 (Prenatal Developmental Toxicity Study). EU Method B.31 (Prenatal Developmental Toxicity Study). EPA OPPTS 870.3700 (Prenatal Developmental Toxicity Study). The experimental start and end date: 6 Oct 2015 - 29 Oct 2015.	Rat, Wistar, 22 mated females per group.	Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide. Degree of purity: 99.5 %. Dose levels: 0, 50, 150 and 500 mg/kg bw/day. Exposure: Oral, gavage, once daily for 7 days per week, from Days 6 to 20 post-coitum, inclusive.	***Maternal findings*** **Mortality** No mortality observed. **Clinical signs** Salivation was observed in 14/22 females at 150 mg/kg and in 19/22 females at 500 mg/kg for one to a few days at the end of treatment. Piloerection and hunched posture were observed in 7/22 respectively in 4/22 females for one to several days at 500 mg/kg. **Body weight** At 500 mg/kg, mean body weight and weight gain, corrected for uterus weight, were lower (-7%, p <0.05 for absolute weight and - 11%, p <0.01 for weight gain) than in controls from Day 9 and onwards, reaching statistical significance on Day 21). **Food consumption** At 500 mg/kg, absolute and relative food consumption were significantly reduced from Day 6 to Day 12 (p <0.01), compared to the controls Afterwards, no differences were seen. **Gross pathology at necropsy** Dark red watery-cloudy contents in the left horn of the uterus observed in one female at 150 mg/kg. **Pregnancy data** One female of the control group, one at 50 mg/kg, two at 150 mg/kg and one at 500 mg/kg delivered early on Day 21. Additionally, one female at 500 mg/kg delivered early on Day 20 Four females were not pregnant; two at 50 mg/kg, one at 150 mg/kg and one at 500 mg/kg. All	Study report, 2016

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, dose levels, duration of exposure	Results	Reference
			other females were pregnant and had litters with viable foetuses. No dose-response related effects on the number of corpora lutea, implantation site, pre- or post-implantation loss, or number of abortions. ***Foetal findings*** **Litter size and sex ratio** No dose-response related effects observed. **Foetal body weight** Body weight was lower in females (mean 4.8 grams) and males (mean 5.0 grams) at 500 mg/kg than in the control group (mean 5.1 and 5.3 grams, resp.). The placenta weights were higher in females (mean 50 grams) and males (mean 52 grams) at 500 mg/kg than in controls (mean 45 and 47 grams, resp.). **External malformations** At 500 mg/kg, two foetuses of the same litter had no tail or a tail that was filamentous. **Visceral malformations** No dose-response related effects observed. **Skeletal malformations and variations** Bent limb bones in 10 foetuses/5 litters (at 500 mg/kg), which was above the upper limit in historical control foetuses (10.6% versus 0.7% per litter, resp.). The foetuses also had one or both scapulae bent and three of them had bent humeri. Bent ribs (mean litter incidence) of 13.5% (control), 23.5% (50 mg/kg), 22.1% (150 mg/kg) and 69.9% (500 mg/kg, p <0.01). Bent limb bones coincided with an increased litter incidence for bent ribs at 500 mg/kg. Reduced ossification of skull (mean litter incidence) of 12.4% (control), 12.5% (50 mg/kg), 21.1% (150 mg/kg) and 45.9% (500 mg/kg, p <0.01). Unossified metatarsals and/or metacarpals (mean litter incidence) of 5.4% (control), 6.6% (50	

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, dose levels, duration of exposure	Results	Reference
			mg/kg), 3.2% (150 mg/kg) and 21.0% (500 mg/kg, p <0.05).	
OECD Guideline 414 (Prenatal Developmental Toxicity Study). EU Method B.31 (Prenatal Developmental Toxicity Study). EPA OPPTS 870.3700 (Prenatal Developmental Toxicity Study). The experimental start and end date: 15 Dec 2017 - 25 Jan 2018.	Rabbit, New Zealand White, 22 time-mated females per group.	Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide. Purity: 99.32%. Dose levels: 0, 10, 30, 100 mg/kg bw/day. Exposure: Oral, gavage, once daily for 7 days a week from Day 6 to Day 28 post-coitum, inclusive.	***Maternal findings*** **Mortality** Two females (30 mg/kg) were euthanized prematurely; One female sacrificed on Day 26 due to lethargic behaviour with hunched posture, piloerection, ptosis, no food intake and body weight loss. At necropsy, intussusception of the caecum was observed. The other female sacrificed on Day 28 due to laboured respiration and gasping. At necropsy, the left caudal lobe of the lungs was perforated, reddish contents of the trachea, dark red foci on the lungs and a reddish, watery-clear fluid in the thoracic cavity was observed. One female at 30 mg/kg and three females at 100 mg/kg were sacrificed prematurely after early delivery (Day 27 and 28). **Clinical signs** No treatment-related clinical signs were noted up to 100 mg/kg. Any clinical signs noted during the treatment period occurred within the range of background findings. **Body weight** No treatment-related body weight or body weight gain changes observed except for a lower body weight gain (corrected for uterus weight) in females at 100 mg/kg compared to controls. The values remained within the historical control range. **Food consumption** No dose-response related effects on absolute or relative food consumption. **Gross pathology at necropsy** Macroscopic observations at necropsy did not reveal any dose-response related alterations. **Pregnancy data** No dose-response related effects on the number of pregnant females, corpora lutea and implantation sites, or pre-and post-implantation loss. One female at 30 mg/kg and three females at 100 mg/kg delivered early on Day 27 or 28. The	Study report, 2018

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, dose levels, duration of exposure	Results	Reference
			females had low to no food consumption in the six days prior to the delivery. Except for cannibalism of two foetuses (one at 30 mg/kg and one at 100 mg/kg), no external abnormalities were observed for the premature litters. ***Foetal findings*** **Foetal body weight** Body weight of females and males (combined) at 100 mg/kg was 5% lower than in controls. **Litter size and sex ratio** Except for cannibalism of two foetuses (one at 30 mg/kg and one at 100 mg/kg), no external abnormalities were observed for the premature litters. No dose-response related effects observed in litter size or sex ratio. **External malformations** Sporadic malformations including carpal and/or tarsal flexures, omphalocele, cyclopia, and meningocele observed in the control, at 10 mg/kg and at 30 mg/kg, but not at 100 mg/kg. **Visceral malformations** Sporadic malformations including abnormal lobation of the liver at 100 mg/kg and mispositioned kidneys and testes in the control, at 10 mg/kg and 30 mg/kg, transposition of the great vessels at 10 mg/kg and narrow aorta and ventricular septum defect in the control group. **Skeletal malformations and variations** Statistically significant increase in incidence of misaligned sternebrae at 100 mg/kg; 9.2% per litter compared to 3.8% in the controls (p <0.05). The value remained within the maximum value of the available historical control data (10.2% per litter).	
OECD Guideline 421 (Reproduction /Developmental Toxicity	Rat, Wistar Han, 10 males and 10 females	Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide. Purity: 99.32%.	***Maternal findings*** **No data available at high dose (600 mg/kg) due to no pregnancies.**	Study report, 2019

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, dose levels, duration of exposure	Results	Reference
Screening Test) – no deviations. EPA OPPTS 870.3550, Reproduction/ Developmental Toxicity Screening Test - no deviations. The experimental start and end date: 16 May 2018 - 20 Sep 2018.	per group.	Dose levels: 0, 60, 200, 600 mg/kg bw/day. Exposure: Oral, gavage, once daily for 7 days a week for a minimum of 12 weeks. Males treated for a min. of 10 weeks prior to mating (covering at least one spermatogenic cycle) and mating (in total 13 weeks or 85-92 days). Females treated for 10 weeks prior to mating (covering at least two estrous cycles), the variable time to conception, the duration of pregnancy and at least 20 days after delivery (in total 18 weeks or 113-127 days). Vehicle: water 1% Aqueous carboxymethyl cellulose.	**Mortality** One female (200 mg/kg) was euthanized on lactation Day 4, due to litter loss. **Clinical signs** No dose-response related changes up to 200 mg/kg. **Food consumption** No dose-response related changes in absolute or relative food consumption up to 200 mg/kg. **Body weight** No dose-response related changes in body weight of females during gestation or lactation up to 200 mg/kg. **Pregnancy data** Pregnant females were 9/10 in the control group (1 female sacrificed prior to mating), 9/10 at 60 mg/kg (1 female with 0 implantation sites), and 10/10 at 200 mg/kg. ***Foetal findings*** **Mortality** One control pup was missing and one pup (60 mg/kg) was found dead at PND 2. One female (200 mg/kg) had lost her single pup on PND 4. **Gestation Index and Duration** Gestation indices were 100% (9/9 in control group), 100% (9/9 at 60 mg/kg) and 90% (9/10 at 200 mg/kg; 1 female had implantations sites only and no live offspring). **Parturition/Maternal Care** No signs of difficult or prolonged parturition. Examination of cage debris revealed no signs of abortion or premature birth. No deficiencies in maternal care observed. **Post-Implantation Survival Index**	

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, dose levels, duration of exposure	Results	Reference
			Post-implantation survival index was 94%, 90% and 85% for control, 60 and 200 mg/kg groups, respectively, all within historical control range. **Litter Size** Nine litters per group containing 95 (mean 10.6), 97 (mean 10.8) and 94 (mean 10.4) living pups of control, 60 and 200 mg/kg groups, respectively. One female at 200 mg/kg had one living pup. Number of culled pups were 26, 25 and 29, respectively. **Live Birth Index** Live birth indices were 97% for pups of control group and 99% for pups at 60 and 200 mg/kg. Two pups of the control group were found dead at first litter check (PND 1). **Viability Index** Viability indices were 99% for the three groups. One control pup was missing and one pup (60 mg/kg) was found dead on PND 2. One female (200 mg/kg) had lost her single pup on PND 4. **Lactation index** All pups from the three groups were alive from PND 4 (after culling) to PND 20 after littering. **Clinical signs** Absence of milk in the stomach at first litter check for two pups (control group) found dead on PND 1, and for one pup (at 60 mg/kg) found dead on PND 2. One pup (200 mg/kg) had swollen circle at the tail apex over PND 13-22. **Body weight of pups** No dose-response related changes in body weight up to 200 mg/kg. **Sex Ratio** At first litter check (PND 1), sex ratio (% of males/females) at 60 and 200 mg/kg was reduced (43/57 and 41/59, resp.) when compared to controls (57/43), reaching statistical significance (p <0.01) at 200 mg/kg. The ratio was non-significant at PND 20 (54/46 for controls, 45/55 at 60 mg/kg, and 47/53 at 200 mg/kg).	

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, dose levels, duration of exposure	Results	Reference
			Anogenital Distance Dose-response related increase in mean anogenital distance, including normalised anogenital distance, in males (2.67 for controls, 2.78 at 60 mg/kg, and 2.93 at 200 mg/kg) and females (1.08 for controls, 1.15 at 60 mg/kg, and 1.19 at 200 mg/kg). **Areola/Nipple Retention** No dose-response related changes in areola/nipple retention up to 200 mg/kg. **Clinical Biochemistry (T4 levels)** No dose-response related changes in serum T4 levels in males or females up to 200 mg/kg. **Gross pathology at necropsy** No dose-response related macroscopic findings up to 200 mg/kg.	

Table 15: Summary table of human data on adverse effects on development

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No data	No data	No data	No data	No data

Table 16: Summary table of other studies relevant for developmental toxicity

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No data	No data	No data	No data	No data

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

Since the adopted opinion by RAC in 2010, three more studies have been conducted on the substance; one oral prenatal developmental toxicity study (OECD 414) in rat (Study report, 2016) and one in rabbit (Study report, 2018), and one oral reproduction/developmental toxicity screening test (OECD 421) in rat (Study report, 2019).

In the **prenatal developmental toxicity study OECD 414** (**Study report, 2016**), the substance was administered to 22 mated female Wistar rats per group at dose levels of 0, 50, 150 and 500 mg/kg bw/day (Day 6 – 20 post-coitum). The control group received the vehicle alone.

Clinical signs at 500 mg/kg included salivation (19/22 females), piloerection (7/22 females), hunched posture (4/22 females). Mean body weight and weight gain (corrected for uterus weight) were lower from Day 9 and onwards in females at 500 mg/kg compared to controls; on Day 21, mean body weight and body weight gain were 7% respectively 11% lower than in controls. Body weight and body weight gain were unaffected at 50 and 150 mg/kg. Mean foetal body weight was (non-significantly) 6% lower at 500 mg/kg than in the control group.

A difference in absolute and relative food consumption were only significantly reduced in females at 500 mg/kg at the beginning of treatment (Day 6 - 12) compared controls. This fully recovered to similar levels as controls from Day 12 onwards. Food consumption was unaffected at 50 and 150 mg/kg.

At 500 mg/kg, ten foetuses from 5 litters were affected with bent limb bones, which was far above the upper limit in historical control foetuses (10.6% versus 0.7% per litter in controls) and therefore considered to be treatment related. The foetuses also had one or both scapulae bent and three of them had bent humeri. Also, the higher incidence of bent limb bones coincided with an increased litter incidence for bent ribs in this group. Bent limb bones were not observed at 50 and 150 mg/kg.

Bent ribs were observed in all groups. A statistically significant increased incidence in bent ribs was observed at 500 mg/kg (mean litter proportions of 69.9% p <0.01 versus 13.5% in controls). Mean litter proportions for this skeletal variation were 23.5% and 22.1% at 50 and 150 mg/kg, respectively.

A significant reduction in ossification of the skull (mean litter incidence of 45.9% p <0.01 versus 12.4% in controls) and increased incidence of unossified metatarsals and/or metacarpals (mean litter incidence of 21.0% p <0.05 versus 5.4% in controls) were reported at 500 mg/kg.

At 50 and 150 mg/kg, the mean litter incidences for reduced ossification of skull were 12.5% and 21.1% per litter and for unossified metatarsals and metacarpals 6.6% and 3.2% per litter, respectively.

External malformations at 500 mg/kg showed two foetuses from the same litter with no tail or a tail that was filamentous, which was confirmed at skeletal examination.

The study author reviewed the findings in the context of the available literature and commented: "In the absence of gross limb malformations, and in the presence of retardation as a consequence of maternal toxicity, bent limb bones could be considered temporary variations rather than malformations. It is hypothesized, that during development the increase in muscle mass puts stress on the bones. If ossification is delayed, the bones might not be able to counteract this pressure and appear bowed until ossification is finalized. Bone development in rats continues long after birth, extending into young adulthood. In a few studies, pups were followed sequentially after birth, and bent long bones and scapulae were transient in nature and appeared normal by the time of weaning"

(De Schaepdrijver *et al*, 2014; Mitchard & French, 2016; Kimmel *et al*, 2014). The study report conclusion was that these were considered transient effects and the registrant (IGM Resins) concurs with this statement. However, the dossier submitter considers that the bent limb bones is not a consequence of maternal toxicity, as there was no marked maternal toxicity reported. Moreover, there were no significant effects on foetal body weights. Since there is no follow up study available for Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide in pups, it is not possible to conclude that the observed effects on limb bones are transient.

It should be noted that, at comparable dose levels to the current study (i.e., 500 mg/kg bw/day compared to 600 mg/kg bw/day), in the OECD TG 421 Reproduction /Developmental Toxicity Screening Test there were no pregnancies and consequently no pups to assess gross limb malformations.

Due to the high incidence of bent limb bones (outside historical control data, and no incidence in the concurrent control) and additional statistically significant increased incidences of skeletal variations, including high incidence of bent rib bones, reduction in ossification of the skull and unossified metatarsals and/or metacarpals seen at 500 mg/kg bw/day in the prenatal developmental toxicity study in rat, a classification in Category 2 should be considered.

In the second **prenatal developmental toxicity study OECD 414** (**Study report, 2018**), the substance was administered to 22 mated female New Zealand rabbits per group at dose levels of 0, 10, 30 and 100 mg/kg bw/day (Day 6 – 28 post-coitum). The control group received the vehicle alone.

The highest dose of 100 mg/kg is considered low in comparison to the effects observed at 500 mg/kg and 600 mg/kg in the rat toxicity study OECD 414 (study report 2016) respectively OECD 421 (study report 2019). According to the study report, the dose was selected based on a previous dose-range finder study with six females per group at dose levels of 100, 200 and 300 mg/kg.

In the dose-range finder study, females dosed at 200 and 300 mg/kg, had 5-11% body weight loss with limited to no food consumption, lean appearance and piloerection. Females at 300 mg/kg also had hunched posture. All females at 300 mg/kg and 3/6 females at 200 mg/kg were sacrificed. The remaining females did not show signs of toxicity. Foetal findings at 200 mg/kg showed reduced litter size (8.7 foetuses/litter) compared to the control group but remained within historical control range.

In the current study, except for four early deliveries (one at 30 mg/kg and three at 100 mg/kg) and cannibalism of 2 (one at 30 mg/kg and one at 100 mg/kg) of the 4 foetuses, no test item related clinical signs, mortality, body weight changes, food consumption changes, gross pathological findings or effects on number of abortions were observed in the maternal animals.

In foetuses dosed at 100 mg/kg, body weight was reduced by 5% and a significant increase in incidence of misaligned sternebrae was observed (9.2% per litter versus 3.8% in controls) but remained within historical control range.

Since the highest dose at 100 mg/kg did not cause any treatment related general toxicity of the maternal animals, the highest dose tested was probably not high enough and it is therefore not possible to conclusively exclude effects of the test item on development in this study.

This difference in maternal/parental tolerability (toxicity) of the substance between rabbits and rats may be the cause of the absence of developmental effects and should be taken into consideration when assessing whether or not a mechanistic mode of action applies between the species.

In the **Reproduction/Developmental Toxicity Screening Test OECD 421** (**Study report, 2019**), the test substance was administered to ten Wistar rats per sex and group at dose levels of 0, 60, 200,

and 600 mg/kg bw/day. The control group received the vehicle alone. The dose levels were selected based on the results of a 90-day repeated dose toxicity study (Study report, 1991).

No females were pregnant at 600 mg/kg possibly due to infertility among the males in this group. Hence, the highest dose for developmental findings was 200 mg/kg bw.

Two pups (one control and one at 200 mg/kg) were missing and one pup (60 mg/kg) was found dead on PND 2. According to the study report, the pups missing were most likely cannibalised.

At 200 mg/kg, gestation index and post-implantation survival index were lower (90% respectively 85%) than in controls (100% respectively 94%). A non-significant dose-response related increase in anogenital distance was observed in males (mean 2.93) and females at 200 mg/kg (mean 1.19) compared to controls (mean 2.67 respectively 1.08). No other developmental toxicity findings including litter size, live birth index, viability index, lactation index, duration of gestation, parturition and maternal care, clinical signs, body weight, areola/nipple retention, T4 thyroid hormone levels and macroscopic examination were observed by treatment up to 200 mg/kg.

10.10.6 Comparison with the CLP criteria

Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide does not meet the criteria for classification as Category 1A because there is no available data in humans.

The criteria for Category 1B are not met because the evidence available in the two OECD 414 studies and the OECD 421 study are not considered as clear evidence of adverse effect on development.

The criteria for classification as Category 2 are met because the high incidence of skeletal malformations and variations seen in the OECD 414 study in rat are considered to be some evidence of developmental toxicity.

10.10.7 Adverse effects on or via lactation

Table 17: Summary table of animal studies on effects on or via lactation

Method, guideline, deviations if any	Species, strain, sex, no/group	Test substance, dose levels, duration of exposure	Results	Reference
OECD Guideline 421 (Reproduction /Developmental Toxicity Screening Test) – no deviations. EPA OPPTS 870.3550, Reproduction/ Developmental Toxicity Screening Test - no deviations. The experimental start and end date: 16 May 2018 - 20 Sep 2018.	Rat, Wistar Han, 10 males and 10 females per group. Weight at study initiation: males 134 - 173 g, females: 105 - 151 g	Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide. Purity: 99.32%. Dose levels: 0, 60, 200, 600 mg/kg bw/day. Exposure: Oral, gavage, once daily for 7 days a week for a minimum of 12 weeks. Males treated for a min. of 10 weeks prior to mating (covering at least one spermatogenic cycle) and mating (in total 13 weeks or 85-92 days). Females treated for 10 weeks prior to mating (covering at least two estrous cycles), the variable time to conception, the duration of pregnancy and at least 20 days after delivery (in total 18 weeks or 113-127 days). Vehicle: water 1% Aqueous carboxymethyl cellulose.	**Lactation index** No difference in number of live offspring after littering (PND 20) compared to after culling (PND 4). No pups found dead/missing between lactation Days 5 and 20, resulting in a lactation index of 100% for all groups. All other results of this study reported in tables 11 and 14 above.	Study report, 2019

Table 18: Summary table of human data on effects on or via lactation

Type of data/report	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No data	No data	No data	No data	No data

Table 19: Summary table of other studies relevant for effects on or via lactation

Type of study/data	Test substance	Relevant information about the study (as applicable)	Observations	Reference
No data	No data	No data	No data	No data

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

In the one-generation reproductive toxicity study (OECD 421) no effect on or via lactation was observed. The number of live offspring on Day 20 after littering compared to the number of live offspring on Day 4 (after culling) was considered not affected by treatment. No pups were found dead/missing between lactation Days 5 and 20, resulting in a lactation index of 100% for all groups.

10.10.9 Comparison with the CLP criteria

There is no evidence to support the classification of diphenyl(2,4,6-trimethylbenzoyl)phosphine in the category for effects on or via lactation.

10.10.10 Conclusion on classification and labelling for reproductive toxicity

Classification of Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide for adverse effects on sexual function and fertility as well as for some evidence of developmental toxicity as Repr. 1B H360Fd is warranted. No classification for adverse effects on or via lactation is warranted.

Specific concentration limits for adverse effects on sexual function and fertility or adverse effects on the development of the offspring are not considered justified since the estimated ED10 values are within the medium potency group (4 mg/kg bw/day < ED10 value < 400 mg/kg bw/day).

RAC evaluation of reproductive toxicity

Summary of the Dossier Submitter's proposal

Adverse effects on sexual function and fertility

The DS summarised that the classification of TPO as Repr. 2, H361f adopted by RAC in 2010 was based on three studies: an oral 28-day repeated dose toxicity study, an oral 90-day repeated dose toxicity study, and a second (non-GLP compliant) oral 28-day and 90-day repeated dose toxicity study. In 2010 RAC concluded that the testes are a target organ in rat (and could potentially lead to reduced male fertility) and that the adverse effects occur in the absence of significant general toxicity. However, due to the limitations of the studies, the evidence was not sufficiently convincing to classify the substance as Category 1B.

In the current proposal an oral reproduction/developmental toxicity screening test (OECD TG 421) was included in addition to the previously assessed studies. Based on this study, the DS concluded that a Category 1B is justified, as the substance exhibits adverse effects on the testes and epididymides, in the absence of marked general toxicity, which lead to reduction in fertility. Reduced weight of the testes and histopathological effects was also noted in the 28-day (Study report, 1989) and 90-day (Study report, 1991) repeated dose toxicity studies.

Adverse effects on development

For the assessment of adverse effects on development the DS included two OECD TG 414 studies (in rat and rabbit) and one OECD TG 421 study in rat. All these studies were performed after the last assessment by RAC in 2010. The DS considered a classification as

Category 2 for developmental toxicity justified based on the high incidence of skeletal malformations and variations seen in the OECD TG 414 study in rat.

Adverse effect on or via lactation

No effects on or via lactation were observed in the OECD TG 421 one-generation reproductive toxicity study, and the DS did not propose any classification.

Comments received during consultation

Three MSCA commented on the proposal, all supported the proposed classification as Repr. 1B, H360Fd. One MSCA asked for consideration of ED10 calculations for potential setting of SCL. The DS responded that the substance can be considered to fall in the medium potency group, and hence no SCL was considered justified.

Assessment and comparison with the classification criteria

Assessment and comparison with the classification criteria

Adverse effects on sexual function and fertility

Since the original classification, **an oral reproduction/developmental toxicity screening test** according to OECD TG 421 has been performed (Study report, 2019), in which, ten Wistar rats per sex and group were exposed to TPO (purity: 99.32%) at dose levels of 0, 60, 200, and 600 mg/kg bw/day by oral gavage. The control group was only administered the vehicle (acetone/olive oil 4:1 v/v). An elongated pre-mating period of 10 weeks was included, to cover at least one complete spermatogenic cycle and at least two complete oestrous cycles.

Two preterm mortalities were reported. In the high dose group, one female was sacrificed *in extremis* during the premating period (day 61) due to animal welfare reasons (moderate lethargy, flat/hunched posture, muscle twitching, piloerection, slight chromodacryorrhoea, slight ptosis, and red snout). 2% body weight loss was noted for this female over Weeks 7-8 of the premating period, followed by recovery in Week 9. Macroscopic examination at necropsy revealed accentuated lobular pattern of liver and reduced size of the spleen. A relationship to treatment could not be excluded as comparable clinical signs were noted for a surviving high dose female as well. In the control group, one female was found dead on day 43. No definite cause of death could be established; however, macroscopic findings could indicate technical error during gavage. If is further noted that one female in the mid dose group was euthanized on PND4 due to a total litter loss during the lactation period.

Clinical signs were only observed in the high dose group, and in addition to the one sacrificed female, they included transient signs of muscle twitching, hunched posture and piloerection in one female while two other females had piloerection. As similar clinical signs were also noted in the high dose female sacrificed in extremis, these observations were regarded as related to treatment. The piloerection was noted for 2 to 3 consecutive days at the end of Week 13 or 16 of treatment. All males in the high dose group showed transient signs of abnormal calm/lethargic behaviour and one male had breathing rales. The clinical signs were short in duration (lasting for only a few minutes), followed by complete recovery.

No change in absolute or relative food consumption was noted in any group. However, a lower mean value for absolute food consumption was observed in the high dose group females from GD14 onwards, which was considered to be related to their non-pregnancy status.

A dose-response related lower body weight and body weight gain were observed in males in the mid- and high dose group during premating and mating period. In the high dose group, a slightly reduced mean body weight gain from start of treatment and onwards was observed in males (reaching statistical significance on Day 8 and from Day 57 onwards), resulting in a 13% lower mean body weight at the end of treatment when compared with controls. In the mid dose group, the reduced mean body weight observed in males at the end of the treatment period was less than 10 % and considered non-adverse. The lower body weight gain noted in females in the high dose group during the gestation period was considered to be related to the non-pregnancy status of all the females, and not reflecting a systemic toxic effect. In the mid dose group, a slightly reduced mean body weight and body weight gain was observed, however, this was considered related to one dam in this group with resorptions.

Macroscopic observations at necropsy revealed alterations in the reproductive organs of males in the high dose group including flaccid testis (8/10 animals) and testis reduced in size (10/10 animals) and epididymides reduced in size (9/10 animals). Further decreased absolute weight and weight relative to body weight of testes and epididymides were noted. Differences between high dose group and control in organ:body weight ratios were 45% and 34% for testes and epididymis, respectively. Microscopic findings were noted in the testes and epididymides in the mid and high dose groups. Massive tubular atrophy was observed in testes in the high dose group. In addition, in the mid dose group atypical residual bodies were observed in 9/10 examined males and single male had degeneration/depletion of germ cells. In the epididymides a massive reduction in sperm numbers were observed in all 10 examined males in the high dose group (see table below).

***Table**: Summary microscopic findings in males, testis and epididymides*

			Dose level (mg/kg/bw/d)			
			0	60	200	600
Testes (10 tissues /dose group)	Atrophy tubular	Massive				10
	Atypical residual bodies	Slight			9	
	Atypical residual bodies	Moderate			1	
	Multinucleated giant cells	Moderate			1	
	Degeneration germ cells	Moderate			1	
	Depletion germ cells	Moderate			1	
Epididymides (10 tissues/dose group)	Cell debris	Minimal				2
		Slight				5
		Moderate			1	1
	Reduced sperm	Slight			1	
		Massive				10

Further microscopic findings were noted in the thyroid gland. Hypertrophy of the follicular cell and the colloid alteration of the thyroid glands were observed in the mid- and high dose group up to a slight degree in males and in females in the high dose group (see table below).

Table: *Summary microscopic findings in males and females, thyroid gland*

			Males				Females			
			Dose level (mg/kg bw/day)							
			0	60	200	600	0	60	200	600
Thyroid glands (10 tissues/dose group)	Hypertrophy follicular cell	Minimal	3	5	2	5	5	3	3	4
		Slight			4	3				2
	Colloid alteration	Minimal			3	2				2
		Slight				4				1

No treatment-related changes were noted in any of the remaining parameters investigated in this study.

In the high dose group, 3 out of 9 females showed no evidence of mating after a prolonged cohabitation period of a total of 21 days with two different males. The mating index in the high dose group was 67% compared with 100% in concurrent control and 99% as mean historical control value. During the mating period, an extended di-oestrus was observed in the 3 high dose females for which mating could not be confirmed. An extended di-oestrus occurred also at low incidence in untreated controls, however, a relation to treatment with the test item could not be excluded.

Table: *reproductive performance/function*

Dose (mg/kg bw/day)	Female/male (number)	In-life reason	Histopathology
0	-	-	-
60	56/16	Not pregnant	-
200	67/27	Total litter loss	
	68/28	Implantation sites only	Testes: moderate degeneration and depletion germ cells
600	72/32 and 36	No evidence of mating	Testes: massive tubular atrophy Epididymides: massive reduced sperm
	74/34 and 38	No evidence of mating	
	79/39 and 40	No evidence of mating	
	71/31	Not pregnant	
	73/33	Not pregnant	
	76/36	Not pregnant	
	77/37	Not pregnant	
	78/38	Not pregnant	
	80/40	Not pregnant	

The fertility index was 100%, 90%, 100 % and 0% for the control, low-, mid-, and high dose group, respectively. In the high dose group 9/9 couples failed to deliver pups, compared to 2/10 in the mid dose group and 1/10 in the low dose group. All males in the high dose group showed massive tubular atrophy in the testes and reduced luminal sperm with luminal cell debris in the epididymides which could explain the lack of offspring. In the mid dose group, one female had a total litter loss while the other female showed implantation sites only. The lack of offspring for the female which had only implantations could be explained by the moderate depletion and degeneration of sperm cells with multinucleated giant cells in the testes and moderate cell debris and slight reduced sperm in the epididymides in the male. The rest of the males in the mid dose group all showed atypical residual bodies, however with no effect on fertility. In the low dose group, the finding of one female which failed to get pregnant could be considered as not related to treatment. In all dose groups, no morphological findings in the reproductive organs of

females related to the treatment were observed. The males in the low dose group did not show any treatment related effect on spermatogenesis.

In the **28-day oral repeated dose toxicity study,** according to a Japanese guideline and GLP (Study report, 1989), TPO (purity 99%) was administered to five Sprague-Dawley rats per sex and group at dose levels of 0, 50, 250, and 750 mg/kg bw/day. The control group was only administered the vehicle (Arachis oil). Two satellite groups, each of five rats per sex were treated with 750 mg/kg bw/day or vehicle alone throughout the 28-day study period and then maintained without treatment for additionally fourteen days.

One female from the satellite high dose group was found dead on Day 4 and one female from the satellite control group died on Day 42 (post-treatment period).

In the high dose group, increased salivation, red/brown staining around the snout and mouth, wet fur, red/brown staining of the fur, hair loss, piloerection, hunched posture, lethargy, ptosis, diuresis, diarrhoea and abdominal distension, and single incidence of vocalisation were observed from Day 3 and onwards. Satellite animals recovered immediately following cessation of dosing and appeared normal throughout the treatment-free period. The mid dose group showed the same clinical signs from day 4 however with less severity and without diarrhoea, abdominal distension, and vocalisation.

In the high dose group body weight and body weight gain was significantly reduced in week four for both males and females. At the end of treatment, body weight was reduced by 5% (mean) in the mid dose group and 14% (mean) in the high dose group compared to controls. Females of the satellite group were not affected, and satellite high dose males quickly recovered during the treatment-free period. A marked reduction in food efficiency was observed during the last week of treatment in the mid and high dose groups. Food efficiency turned back to normal in the 750 mg/kg satellite group following cessation of treatment.

Decreased testes weight (mean absolute weight 3.09 grams and mean relative weight 0.91) compared to controls (mean absolute weight 3.39 grams and mean relative weight 1.04) and size, microscopically identified as testicular atrophy, was observed in all high dose males. Grading showed increased severity of testicular atrophy at the high dose. Although one animal from each of the remaining treatment group also had a minimal degree of testicular atrophy, the study author considered it to be spontaneous in origin and unrelated to treatment at these dose levels. Testicular atrophy was also present amongst males in the satellite group (750 mg/kg), although the incidence was reduced (3/5).

In the **90-day oral repeated dose toxicity study** similar to OECD TG 408, GLP (Study report, 1991), the test substance (purity 94.8%) was administered by gavage once daily (5 days/week) to ten Wistar rats per sex and group at dose levels of 0, 100, 300, or 1000 mg/kg bw/day. The control group received the vehicle (CMC (carboxymethyl cellulose), 0.5% in water) alone.

Females in the high dose group showed a reduced general state of health, and two females in this group died on day 44 and 48. There were no mortalities or severe clinical signs reported in males in any dose group. The body weight and body weight gain were reduced in females (8 % and 16 %, respectively) and in males (23 % and 38 %, respectively) in

the high dose group compared to control animals, while in the mid dose group reduction was only observed in males (10 % and 16 %, respectively) compared to the control group.

In males in the mid- and high dose group, the testes were reduced in size from week 6 and onwards. The absolute and relative testes weights were decreased, on average by about 50% in all males in these dose groups compared to control animals.

All males in the mid and high dose group had moderate to marked degree of diffuse atrophy of the testicular parenchyma and a slight to moderate degree of interstitial oedema. In the low dose group one male exhibited moderately reduced spermiogenesis. All males of this dose group showed a minimal to moderate vacuole degeneration of spermatogonia in some seminiferous tubules. These lesions and the focal atrophy findings were also seen in the control group up to the same grading and were not considered to be substance related by the study author.

In the **second 28-day oral repeated dose toxicity study** similar to OECD TG 407, not GLP (Study report 2001), three male Wistar rats were exposed to 0 or 1000 mg TPO/kg bw/day (purity: 99.3%) by gavage. The controls received the vehicle (CMC,) 0.5% in water) alone. Age at study initiation was between 41-43 days. No testicular effects, mortalities or clinical signs were reported.

In the **second 90-day oral repeated dose toxicity study** similar to OECD TG 408, not GLP (Study report, 2001), ten Wistar rats were exposed to 0 or 1000 mg TPO/kg bw/day (purity: 99.3%) by oral gavage. The controls received the vehicle (CMC, 0.5% in water) alone. Age at study initiation was 34 days. No mortalities or adverse clinical signs were reported. Body weight in the exposed animals was reduced by 10% compared to the controls. In 8/10 males, testes were reduced in size and loss of turgor was observed. Mean testes weights were significantly lower in the exposed rats (mean absolute weight 2.1 grams and mean relative weight 0.718 %) compared to the control group (mean absolute weight 3.286 grams and mean relative weight 0.996 %). All testes showed slight to severe degree of diffuse atrophy of seminiferous tubules. In 8/10 males, epididymides was reduced in size and histopathology revealed oligo- to azoospermia (*i.e.* reduction or absence of mature sperms). Four males had oedema and Leydig cell hyperplasia of minimal to slight degree.

In summary, the current harmonised classification of TPO as Repr. 2 (H361f), adopted by RAC in 2010, is based on an oral 28-day repeated dose toxicity study, an oral 90-day repeated dose toxicity study and the non-GLP compliant oral 28-day and 90-day repeated dose toxicity study showing reduced weight of the testes and histopathological effects. If was concluded that the testes are a target organ in rat and that the adverse effects occur in the absence of marked general toxicity.

In the more recent oral reproduction/developmental toxicity screening test according to OECD TG 421 (Study report, 2019) with doses up to 600 mg/kg bw/day adverse effects on testis and epidiymides was observed in the absence of marked general toxicity. The fertility index in the high dose group of 600 mg/kg bw/day was 0% and all the males in this dose group showed massive tubular atrophy in the testes and reduced luminal sperm with luminal cell debris in the epididymides.

Overall, a classification as Repr. 1B for adverse effects on sexual function and fertility is appropriate based on clear evidence of adverse effects on the testes and epididymides, in the absence of marked general toxicity, which lead to reduction in fertility.

In conclusion, RAC is of the opinion that a classification of TPO as Repr. 1B; H360F is justified.

Adverse effects on development

TPO is currently not classified for adverse effects on development. Three studies have been conducted with the substance since the previous assessment by RAC in 2010; one oral prenatal developmental toxicity study (OECD TG 414) in rat (Study report, 2016) and one in rabbit (Study report, 2018), and one oral reproduction/developmental toxicity screening test (OECD TG 421) in rat (Study report, 2019).

In the prenatal developmental toxicity study OECD TG 414 (Study report, 2016), TPO (purity 99.5%) was administered by gavage to 22 mated female Wistar rats per group at dose levels of 0, 50, 150 and 500 mg/kg bw/day (Gestation Day (GD) 6–20). The control group received the vehicle alone (CMC, 1% in water). No mortalities were observed. Clinical signs in the high dose group included salivation (19/22 females), piloerection (7/22 females), hunched posture (4/22 females). Mean body weight and corrected body weight gain were 7% and 11%, respectively, lower than in controls on day 21 in the high dose group, while unaffected in the low- and mid-dose groups. Food consumption was significantly reduced Day 6 to 12 in the high dose group compared to controls, however fully recovered to similar levels as controls from Day 12 onwards. No effect on food consumption was observed in the low and mid dose groups. Four animals were not pregnant, two at 50 mg/kg bw/day, one at 150 mg/kg bw/day and one at 500 mg/kg bw/day. All other females were pregnant and had litters with viable foetuses. Mean litter size (viable foetuses) was 10.6, 10.2, 9.7 and 10.1 in control, low-, mid- and high-dose group respectively. No effects on the number of corpora lutea, implantation sites, and pre- and post-implantation loss was reported up to 500 mg/kg bw/day.

Mean foetal body weight was 6% lower in the high dose group compared to controls, the reduction in foetal weight was significant for females, but not for males. No effect was observed on sex ratio, litter size or litter weight in all dose groups.

External malformations were observed in two foetuses from the same litter in the high dose group. One foetus had no tail, and one foetus has a filamentous tail. Skeletal malformations were observed in the high dose group evident as bent limb bones in 10 foetuses from 5 litters compared to one control foetus. In all cases one or both scapulae were bent and in three foetuses also humeri were involved. Bent limb bones were not observed in the low- and mid-dose group. The finding in the high dose group (10.6% per litter) was far above the upper limit in historical control foetuses (0.0-0.7% per litter based on 5 studies from 2014-2015). The higher incidence of bent limb bones coincided with an increased litter incidence of bent ribs with 13.5%, 23.5%, 22.1% and 69.9% per litter in control, low-, mid-, and high dose group, respectively. The incidence of bent ribs in the high dose group was statistically significantly different from the controls, and all foetuses with bent limb bones in the high dose group also had bent ribs.

Skeletal variations were also observed in the high dose group. The ossification of the scull and unossified metatarsals and metacarpals were statistically significantly reduced compared to the controls. Reduced ossification of the skull had a mean litter incidence of

45.9% (p <0.01) in the high dose group versus 12.4% in controls. The increased incidence of unossified metatarsals and/or metacarpals showed a mean litter incidence of 21.0% (p <0.05) in the high dose group versus 5.4% in controls.

***Table**: Foetal malformations and variations*

% per litter	0 mg/kg bw/day	50 mg/kg bw/day	150 mg/kg bw/day	500 mg/kg bw/day	Historical control data***, % per litter (foetuses/litters)
Malformations					
No tail or filamentous tail[a]	0	0	0	0.7 % (2 foetus/1 litter	0.0% (0/0)
Bent limb bones[b]	0.8 % (1 foetus/1 litter)	0	0	10.6% (10 foetus/5 litters)	0.0-0.7% (1/1)
Variations					
Bent ribs[b]	13.5 %	23.5%	22.1%	69.9% **	0.8-7.7% (34/17)
Reduced ossification of scull bones[b]	12.4 %	12.5 %	21.1 %	45.9 %**	0.0-1.4% (6/4)
Unossified metatarsals and metacarpals[b]	5.4 %	6.6 %	3.2 %	21 % *	0.0-3.7% (18/11)

* Significantly different from control at 0.05
** Significantly different from control at 0.01
*** Historical control data from 5 studies, 2014-2015.
[a]: measured in approx. 200 foetuses/20 litters
[b]: measured in approx. 100 foetuses/20 litters

In the publications by De Schaepdrijver *et al*. (2014), Mitchard & French (2011) and Kimmel *et al*. (2014) it has been discussed if bent limb bones should be considered as a temporary variation rather than malformation. All these three publications indicated that the finding of bent limb bones could be transient in nature and should be considered as a variation rather than a malformation. During the general consultation two additional studies by Hofmann *et al.* (2016) and Mitchard and Stewart (2014) were provided. In the study by Mitchard and Stewart (2014) Wistar Hannover rats were exposed from GD6 to GD17, and it was reported that skeletal abnormalities were evident in the foetuses at GD20, however not in pups assessed at PND21 and concluded that these malformations should be regarded as minor rather than major. In the review by Hofmann *et al*. (2016) it was concluded that the data assessed uniformly show that bent scapulae and bent long bones are transient, and not permanent foetal changes, that are completely repaired postnatally and that they should be classified as variations rather than malformations. RAC notes that all these studies have been performed in relation to the regulation of pharmaceuticals and has to be considered in this context.

The bent limb bones observed in the OECD TG 414 study in rats are not considered to be a consequence of maternal toxicity, as there was no marked maternal toxicity reported. In addition, no significant effects on foetal body weights were observed. Furter, there is no follow up study available following the pups postnatally, and it is therefore not possible to assess a possible transient nature of the observed effects on limb bones.

RAC therefore considers that the finding of bent limb bones and the statistically significant increased incidences of skeletal variations, including bent ribs, reduction in ossification of skull bones and unossified metatarsals and/or metacarpals in the high dose group which

were outside historical control data, is relevant for a classification for adverse effects on development. These effects were observed in the absence of marked maternal toxicity.

In the second prenatal developmental toxicity study OECD TG 414 (Study report, 2018), TPO (purity 99.32%) was administered by gavage to 22 mated female New Zealand rabbits per dose group of 0, 10, 30 and 100 mg/kg bw/day on gestation day (GD) 6–28. The control group received the vehicle alone (CMC, 1% in water).

The selection of dose levels was based on a dose-range finder study with six females per group at dose levels of 100, 200 and 300 mg/kg bw/day. In this study, females dosed at 200 and 300 mg/kg bw/day, had 5-11% body weight loss with limited to no food consumption, lean appearance and piloerection. Females at 300 mg/kg bw/day also had hunched posture. All females at 300 mg/kg bw/day and 3/6 females at 200 mg/kg bw/day were sacrificed. The remaining females did not show signs of toxicity. Foetal findings at 200 mg/kg bw/day showed reduced litter size (8.7 foetuses/litter) compared to the control group but remained within historical control range.

In the main study two females in the mid-dose groups were euthanized prematurely on GD 26 (female 64) and GD 28 (female 49) respectively. At necropsy female 64 showed intussusception of the caecum with dark red discolouration, which could be a chance finding. Female 49 showed perforation of the left caudal lobe of the lungs which could be related to a dosing related incidence. Further, one female in the mid-dose group and three females in the high dose group were sacrificed prematurely due to early deliveries (GD 27 or 28). Two foetuses (one in the mid-dose group and one in the high dose group) were cannibalised. No external abnormalities were observed for the preterm litters.

No treatment related maternal clinical signs were observed up to the highest dose. Further, no effect was observed on maternal body weight gain. The corrected maternal body weight gain was slightly lower in the high dose group compared to controls, however not statistically significantly different. Further, no effects were observed on food consumption, gross pathology or number of abortions. Number of gravid females were 21 in the control group and 18 in all dosed groups.

No effects on sex ratio, litter size or litter weight. Mean litter size (viable foetuses) was 9.1, 9.1, 9.1 and 9.5 in control, low-, mid- and high-dose group, respectively. However, the foetal body weight was reduced by 5% in the high dose group.

External malformations were observed in the control, low- and mid-dose group in two, three and one foetus(es) respectively. No external malformations were observed in the high dose group. Skeletal variations were observed as a statistically significantly increase in the incidence of malaligned sternebrae in the high dose group (9.2% per litter compared to 3.8% in the controls). However, the finding in the high dose groups is within the historical control data (2.9-10.2% per litter based on 4 datasets, 2013-2017).

Sporadic visceral malformations were observed in the control and all dose groups, including abnormal lobation of the liver in the high dose group, malpositioned kidneys and testes in control, low- and mid-dose group, transposition of the great vessels in the low dose group and narrow aorta and ventricular septum defect in the control group.

RAC is of the opinion that the malformations observed is incidental and not related to treatment due to the absence of a dose-response relationship, observed frequencies and that the skeletal malformation observed was within the historical control data range.

It is noted that the highest dose of 100 mg/kg was not sufficiently high to cause treatment related general toxicity of the maternal animals, and RAC considers that this study is inconclusive regarding effects of the test item on development in rabbits.

In the **Reproduction/Developmental Toxicity Screening Test** according to OECD TG 421 (Study report, 2019), TPO (purity 99.32%) was administered to ten Wistar rats per sex and group at dose levels of 0, 60, 200, and 600 mg/kg bw/day. The control group received the vehicle alone (acetone/olive oil 4:1 v/v).

In the high dose group, no females were pregnant, and the highest dose for assessment of developmental findings was therefore the mid dose group of 200 mg/kg bw/day where no clinical signs, no dose-response related changes in absolute or relative food consumption and no dose-response related changes in body weight of females during gestation or lactation were observed. Pregnant females were 9/10 in the control group (1 female sacrificed prior to mating), 9/10 in the low dose group (1 female with 0 implantation sites), and 10/10 in the mid dose group. One female in the mid dose group was euthanized on lactation Day 4, due to litter loss.

As regards foetal findings, one control pup and one pup in the low dose group was missing or found dead at PND 2. In addition, one female in the mid dose group lost her single pup on PND 4. The gestation index was 100% (9/9) in the controls, 100% (9/9) in the low dose group and 90% (9/10) in the mid dose group. The post-implantation survival index was 94%, 90% and 85% for control, low and mid dose group, respectively, and all were within the historical control range.

Dose-response related, but not statistically significant, increase in mean/corrected anogenital distance, in males (2.67/1.42 for controls, 2.78/1.47 at 60 mg/kg, and 2.93/1.54 at 200 mg/kg) and females (1.08/0.59 for controls, 1.15/0.62 at 60 mg/kg, and 1.19/0.64 at 200 mg/kg) was observed.

No other developmental toxicity findings including litter size, live birth index, viability index, lactation index, duration of gestation, parturition and maternal care, clinical signs, body weight, areola/nipple retention, T4 thyroid hormone levels and macroscopic examination were observed by treatment up to 200 mg/kg.

In summary, the developmental toxicity study in rats is relevant for a classification for adverse effects on development based on the finding of skeletal malformations including bent limb bones and the statistically significant increased incidences of skeletal variations, including bent ribs, reduction in ossification of skull bones and unossified metatarsals and/or metacarpals in the high dose group which were outside historical control data, and observed in the absence of marked maternal toxicity.

RAC notes that the developmental toxicity study in rabbits did not show any effects relevant for classification, however, the tested doses were considered not sufficiently high to cause treatment related general toxicity in the maternal animals.

Furthermore, in the OECD TG 421 screening test in rats, where no females were pregnant at 600 mg/kg bw/day, the highest dose for assessment of developmental findings was the

mid dose of 200 mg/kg bw/day which limits the assessment for developmental toxicity. The only developmental effect observed was a dose related, however, not statistically significant increase in anogenital distance.

Overall, a classification as Repr. 2 for adverse effects on development is appropriate based on some evidence of adverse effects including increased incidence of skeletal malformations and variations in rats, in the absence of marked general toxicity.

RAC considers that a classification of TPO as Repr. 2; H361d is justified.

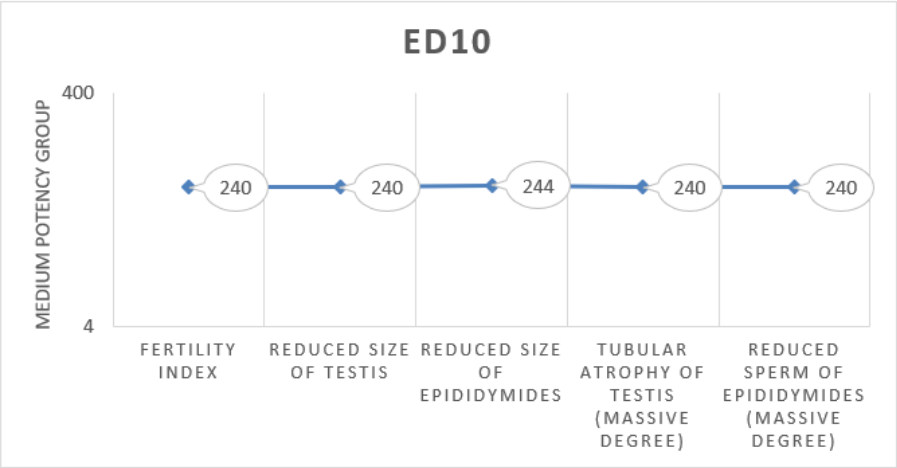
In conclusion, RAC is of the opinion that **TPO warrants classification as Repr. 1B; H360Fd.**

Calculation of ED10-value for assessment of SCL-setting for adverse effects on sexual function and fertility

The DS calculated the ED10-values based on the effects on fertility and reproductive organs observed In the OECD TG 421 study in rats (Study report, 2019). The calculations were performed in accordance with the ECHA Guidance on the Application of the CLP criteria (v.5.0, 2017).

For fertility index an interpolation between the NOAEL (100% at 200 mg/kg bw/day) and LOAEL (0% at 600 mg/kg bw/day) results in a ED10 of 240 mg/kg bw/day based on the following calculation: (600-200) / (100-0) = 4.0 mg/kg per % (steepness). Going from 100% to 90% requires subtraction of 10%. This equals 10% x 4.0 mg/kg per % = 40 plus 200 as the starting point = 240 mg/kg bw/day.

***Figure**: ED10-values calculated from effects observed in the OECD TG 421 study in rats.*



The ED10-values all fall within the medium potency group (4 mg/kg bw/day < ED10-value < 400 mg/kg/bw/day), and hence for a classification in category 1B for adverse effects on sexual function and fertility, the GCL of 0.3% should apply.

Modifying factors are not considered relevant to apply in this case since the calculated ED10-values are not borderline to a higher or lower potency group.

Overall, RAC is of the opinion that no SCL is appropriate based on the ED10 values calculated, and the GCL should apply.

Calculation of ED10-value for assessment of SCL-setting for adverse effects on development

ED-10 value for adverse effects on development was calculated based on the effect on bent limb bones observed in the OECD TG 414 study in rats (Study report, 2016). The calculations were performed in accordance with the ECHA Guidance on the Application of the CLP criteria (v.5.0, 2017).

For bent limb bones the highest tested dose of 500 mg/kg bw/day show an incidence of 10.6% while the incidence in controls is 0.8%. The ED10 is defined as the dose level at which 10% of the test population above the incidence in the concurrent control shows the effect, indicating that in this case the ED10 is approximately 500 mg/kg bw/day (10.6%-0.8%= 9.8%). On this basis the substance could be considered falling into the low potency group for a category 2 classification with an ED10 above 400 mg/kg bw/day. The SCL for the low potency group should be in the range of 3-10%. The limit of 10% may according to ECHA Guidance on the Application of the CLP criteria be considered in certain cases, such as for substances with a ED10 value above 1000 mg/kg bw/day and a NOAEL below 1000 mg/kg bw/day. In this case the ED10 is well below 1000 mg/kg bw/day, and the NOAEL is 150 mg/kg bw/day. A SCL of around 3 % could be considered, however as this is similar to the GCL, no SCL is proposed. This is further supported by assessing the ED10 values for the variations observed in the OECD TG 414 in rats which were calculated to be well below 400 mg/kg bw/day. E.g. calculations based on reduced ossification of scull bones indicate an ED 10 to be approximately 150 mg/kg bw/day or slightly higher (21.1% at 150 mg/kg bw/day-12.4% at 0 mg/kg bw/day =8.7%).

Modifying factors are not considered relevant to apply in this case since the calculated ED10-values are not borderline to a higher or lower potency group.

Overall, RAC is of the opinion the GCL of 3% should be used for adverse effects on development.

Effects on or via lactation

In the OECD TG 421 an oral reproduction/developmental toxicity screening test (Study report, 2019), no adverse effect on or via lactation was observed. No effect was observed on the number of live offspring on Day 20 after littering compared to the number of live offspring on Day 4 (after culling). Further, no pups were found dead/missing between lactation Days 5 and 20.

Overall, RAC is of the opinion that no classification is warranted for effects on or via lactation.

10.11 Specific target organ toxicity-single exposure

Not evaluated in this CLH-proposal.

10.12 Specific target organ toxicity-repeat exposure

Not evaluated in this CLH-proposal.

10.13 Aspiration hazard

Not evaluated in this CLH-proposal.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

Not evaluated in this CLH-proposal.

12 EVALUATION OF ADDITIONAL HAZARDS

Not evaluated in this CLH-proposal.

13 ADDITIONAL LABELLING

Not relevant.

14 REFERENCES

Study report (2012) as summarised in the publicly disseminated REACH Registration for Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide https://echa.europa.eu/registration-dossier/-/registered-dossier/13110 accessed 27 May 2020 - Study report (2012) in Annex I.

Study report (2019) as summarised in the publicly disseminated REACH Registration for Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide https://echa.europa.eu/registration-dossier/-/registered-dossier/13110 accessed 27 May 2020 - Study report (2019a) in Annex I.

Study report (2016) as summarised in the publicly disseminated REACH Registration for Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide https://echa.europa.eu/registration-dossier/-/registered-dossier/13110 accessed 27 May 2020 - Study report (2016) in Annex I.

Study report (2018) as summarised in the publicly disseminated REACH Registration for Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide https://echa.europa.eu/registration-dossier/-/registered-dossier/13110 accessed 27 May 2020 - Study report (2018) in Annex I.

Study report (1989) as summarised in the publicly disseminated REACH Registration for Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide https://echa.europa.eu/registration-dossier/-/registered-dossier/13110 accessed 27 May 2020 - Study report (1989d) in Annex I.

Study report (1991) as summarised in the publicly disseminated REACH Registration for Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide https://echa.europa.eu/registration-dossier/-/registered-dossier/13110 accessed 27 May 2020 - Study report (1991) in Annex I.

Study report (2001) as summarised in the publicly disseminated REACH Registration for Diphenyl(2,4,6-trimethylbenzoyl)phosphine oxide https://echa.europa.eu/registration-dossier/-/registered-dossier/13110 accessed 27 May 2020 - Study report (2001) in Annex I.

De Schaepdrijver L., Delille P., Geys H., Boehringer-Shahidi C. & Vanhove C. (2014) In vivo longitudinal micro-CT study of bent long limb bones in rat offspring. Reprod Toxicol 46, 91–97.

Mitchard T.L. & French J. (2011) Apparent postnatal recovery of chondrodystrophy in the Harlan Han Wistar rat. Reprod Toxicol 32, 169–70.

Kimmel C.A., Garry M.R., DeSesso J.M. (2014) Review Article: Relationship Between Bent Long Bones, Bent Scapulae, and Wavy Ribs: Malformations or Variations? Birth Defects Research (Part B) 101:379–392.

Additional references
Hofmann et al. (2016) Postnatal Fate of Prenatal-induced Fetal Alterations in Laboratory Animals, Reproductive Toxicology, 61, 177–185
Mitchard and Stewart (2014) Reduced post-natal versus pre-natal incidence of bent long bones and scapulae in a preliminary investigation using the Han Wistar rat, Reproductive Toxicology, 45, 39-44.

15 ANNEXES

Annex I – non-confidential data.