Ministry of Environment and Food of Denmark
Environmental Protection Agency

SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

4,4'-Isopropylidenediphenol, propoxylated

EC No 500-097-4

CAS No 37353-75-6

Evaluating Member State: Denmark

Dated: 17 April 2020

Template Version 2.1
March 2015

Evaluating Member State Competent Authority

Danish Environmental Protection Agency
Tolderlundsvej 5
5000, Odense C
Denmark
Tel: +45 72 54 40 00
Email: mst@mst.dk
Contact person: Asger Bolwig
Tel: +45 22 39 56 52
Email: asbol@mst.dk

Year of evaluation in CoRAP: 2013

Before concluding the substance evaluation a Decision to request further information was issued on: 31 August 2015. The requested information was received 04/09/2018.

Further information on registered substances here:

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

DISCLAIMER

This document has been prepared by the evaluating Member State as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006. The information and views set out in this document are those of the author and do not necessarily reflect the position or opinion of the European Chemicals Agency or other Member States. The Agency does not guarantee the accuracy of the information included in the document. Neither the Agency nor the evaluating Member State nor any person acting on either of their behalves may be held liable for the use, which may be made of the information contained therein. Statements made or information contained in the document are without prejudice to any further regulatory work that the Agency or Member States may initiate at a later stage.

Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process, the Member States perform the evaluation and ECHA secretariat coordinates the work. The Community rolling action plan (CoRAP) of substances subject to evaluation, is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. The document consists of two parts i.e. A) the conclusion and B) the evaluation report. In the conclusion part A, the evaluating Member State considers how the information on the substance can be used for the purposes of regulatory risk management such as identification of substances of very high concern (SVHC), restriction and/or classification and labelling. In the evaluation report part, B the document provides explanation how the evaluating Member State assessed and drew the conclusions from the information available.

With this Conclusion document the substance evaluation process is finished and the Commission, the Registrant(s) of the substance and the Competent Authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes. Further analyses may need to be performed which may change the proposed regulatory measures in this document. Since this document only reflects the views of the evaluating Member State, it does not preclude other Member States or the European Commission from initiating regulatory risk management measures which they deem appropriate.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

Contents

Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

4,4'-Isopropylidenediphenol, propoxylated (BPAPO) was originally listed on CoRAP and selected for substance evaluation in order to clarify concerns about:

- Suspected CMR (fertility and developmental toxicity)

- Exposure/wide dispersive use

- Aggregated tonnage.

During the evaluation also other concerns were identified. These additional concerns were:

- Endocrine disruption (human health)

- Developmental toxicity (developmental neurotoxicity and developmental immunotoxicity).

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

The substance is not known to be under any other EU regulatory process

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the substance has led the evaluating Member State to the following conclusions, as summarised in the table below.

Table 1

CONCLUSION OF SUBSTANCE EVALUATION Conclusions	Tick box
Need for follow-up regulatory action at EU level	
Harmonised Classification and Labelling	
Identification as SVHC (authorisation)	
Restrictions	
Other EU-wide measures	
No need for regulatory follow-up action at EU level	X

Conclusions of the substance evaluation:
Based on the available data, the eMSCA has decided not to request further tests and not to suggest further regulatory risk management measures at present.

4. FOLLOW-UP AT EU LEVEL

4.1. Need for follow-up regulatory action at EU level

Not applicable.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

5.1. No need for regulatory follow-up at EU level

Table 2

REASON FOR REMOVED CONCERN The concern could be removed because	Tick box
Clarification of hazard properties/exposure	X
Actions by the registrants to ensure safety, as reflected in the registration dossiers (e.g. change in supported uses, applied risk management measures, etc.)	

The results obtained from the requested studies indicate that some endpoints of concen under substance evaluation of BPAPO are indeed affected including the thyroid system, cholesterol levels and estrous cyclicity. The specific mechanisms and modes of action for which BPAPO affects these endpoints are presently unknown.
No decisive effects were seen on fertility and only non-consistent findings were reported in the requested EOGRTS and 90-day. In the PNDT-study, developmental effects were observed but only at doses that also caused marked maternal toxicity. Due to inconsistent findings and lack of effects observed in the Functional Observation Battery, it is concluded by the eMSCA that the concern for developmental neurotoxicity and developmental immunotoxicity has been clarified and that no further action is required for these endpoints. The eMSCA is of the opinion that significant increases in cholesterol levels observed in both the 90-day study and in the EOGRTS were treatment-related and may be connected to the body weight increases observed in females but the underlying mechanism is presently unknown.
Several endpoints of concern were not adversely affected in the requested studies including nipple retention and anogenital distance which are considered to be sensitive endpoints for endocrine disruption.
In conclusion, the eMSCA considers the results to be ambiguous as adverse effects were not seen across all endpoints, dose groups and cohorts and no clear adverse outcome pathway could be established. Furthermore, the eMSCA has not identified further tests that would further clarify these concerns. The eMSCA also does not consider the adverse effects observed to be sufficiently severe to trigger further regulatory risk management measures at present. Therefore, the eMSCA concludes that there is no apparent need for follow-up action at EU level at this time. However, the eMSCA is aware that the on-going work in the Bispenols Ad-Hoc Working Group (established under the Risk Management and Evaluation Platform (RiME+)) may bring new information to light, as may future knowledge on mechanism and development of test guidelines. The residual concern on BPAPO may therefore need revisiting in the future.

5.2. Other actions

There are some uncertainties about the possible content of BPA in BPAPO. This is currently being investigated by the working group on bisphenols and its derivatives. Depending on the outcome of the ongoing work in this group, further regulatory action(s) might be necessary. If the substance contains more than 0.1 % unreacted BPA then the substance can be regulated directly on this basis as a substance of very high concern (SVHC). At present, it is therefore recommended that registrants of BPAPO should strive for minimisation of residual BPA in BPAPO to mitigate the hazard/risk arising from BPA.

6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

Not applicable, see section 5.

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

4,4'-Isopropylidenediphenol, propoxylated was originally selected for substance evaluation in order to clarify concerns about:

- Suspected CMR (fertility and developmental toxicity)

- Exposure/wide dispersive use

- Aggregated tonnage.

During the evaluation also other concerns were identified. These additional concerns were:

- Endocrine disruption

- Developmental toxicity (developmental neurotoxicity and developmental immunotoxicity).

Table 3

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome / conclusion**
Reproductive toxicity	Ambigous but currently no further action – please see section 7.9.7
Exposure	Concern clarified – no further action
Endocrine disruption	Ambigous but currently no further action – please see section 7.9.7
Developmental toxicity	Concern clarified – no further action.

7.2. Procedure

BPAPO was included in the Community rolling action plan (CoRAP) for substance evaluation to be evaluated in 2013. The updated CoRAP was published on the ECHA website on 20 March 2013.

The justification for initial grounds for concern leading to the CoRAP nomination of BPA PO was based on estrous cyclicity disorders observed in a Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OECD TG 422).

In the course of the evaluation, additional concerns for endocrine disruption (and developmental toxicity – specifically developmental neurotoxicity and developmental immunotoxicity) were identified.

Following the substance evaluation, a decision was sent to the registrant 31 August 2015 requiring the registrant to submit the following information.

- Extended one-generation reproductive toxicity study in rats, oral route (OECD TG 443) including extension of Cohort 1B to produce the F2 generation and including Cohorts 2A and 2B for developmental neurotoxicity and Cohort 3 for developmental immunotoxicity with the grade BPA 4PO

- Pre-natal developmental toxicit study (OECD TG 414) in rats or rabbits, oral route with the grade BPA 4PO

- Sub-chronic toxicity study (90-day), oral route (OECD TG 408) in rats with the grade BPA 4PO

- Stably transfected transactivation *in vitro* assays to detect oestrogen receptor agonists (OECD TG 455) with the grades BPA 2PO, BPA 3PO, BPA 4PO and BPA 5PO.

- Information on the registered substance to be reflected in the CSR including information on personal protective equipment, documentation that risks to workers and consumers are adequately controlled for all exposure scenarios and documentation supporting the claim that releases to the environment from recycling of paper is negligible.

The deadline to provide the information was 7 September 2018.

Following submission of the requested studies, the second phase of evaluation was initiated and the initial evaluation was updated to consider information provided in response to the SEv decision. The follow-up evaluation conducted by the eMSCA led to the conclusions detailed in part A.

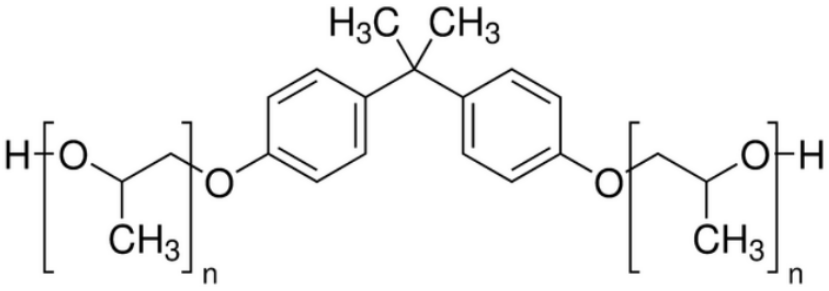
7.3. Identity of the substance

Table 4

SUBSTANCE IDENTITY	
Public name:	4,4'-propane-2,2-diyldiphenol, polymer with 2-methyloxirane
EC number:	500-097-4
CAS number:	37353-75-6
Index number in Annex VI of the CLP Regulation:	
Molecular formula:	C15H16O2.(C3H6O)n n = 1 to 4.5
Molecular weight range:	> 286.0 — < 518.0
Synonyms:	Propoxylated Bisphenol A BPA PO BPA PO 1 - 4.5 PO

Type of substance ☐ Mono-constituent ☐ Multi-constituent ☒ UVCB

Structural formula:



n = 1 – 4.5

Multiconstituent / UVCB substance / others

BPA PO is composed of constituents with a BPA backbone but with different chain lengths of propoxylated groups on each side of the molecule. The structural information in the registration dossier is judged to be sufficient for identification of the constituents.

A number of representative SMILES strings have been generated by the evaluating MSCA and is presented in Table 6. The concentration of each constituent in the substances varies and the substance can be divided into different *grades* depending on the mean chain length of the constituents. A more detailed description, including quantitative compositional information for two different grades, BPA 3PO (UVCB) and BPA 5PO (UVCB), is available in the registration dossier. Since this information is not publicly available, it has been included in the confidential Annex 1 to this substance evaluation report. In this regard it is important to notice the difference between the two *grades* BPA 3PO (UVCB) and 5PO (UVCB) which are UVCB's and the *monoconstituents* BPA 3PO and 5PO which appears as constituents in in the registered substance.

7.3.1 Identity of structural related substance

The Registrant(s) have used read-across to a structural analogue in the registration dossier for BPA PO. This structural analogue is a monoconstituent substance, BPA 2PO that also appears as a constituent in BPA PO. BPA 2PO has been registered under REACH with a full registration in the tonnage band 1,000 to 10,000 Tpa.

A read-across justification document has been submitted by the Registrant(s) and is attached in Section 13 of the IUCLID file. Since this document is not publicly available, and therefore has to be considered as confidential, the evaluating MSCA have included the assessment of the read-across justification in a separate confidential Annex 2 to this substance evaluation report.

Table 5: Substance identity of the structural analogue BPA 2PO

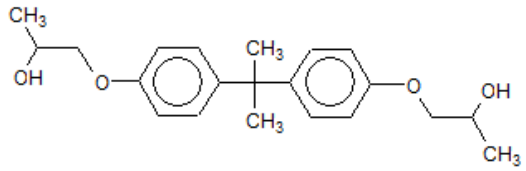
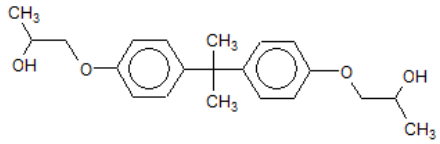
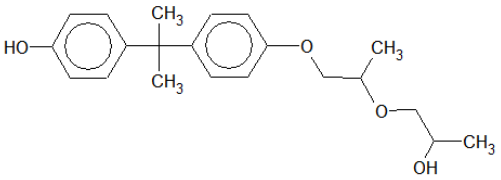
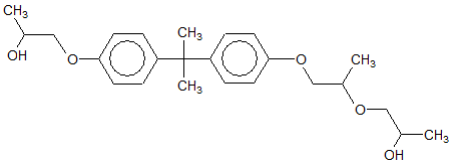
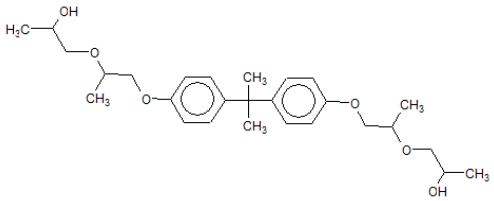
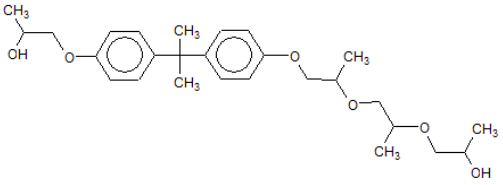
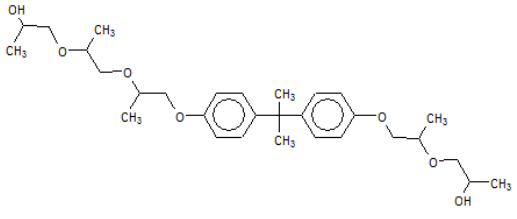
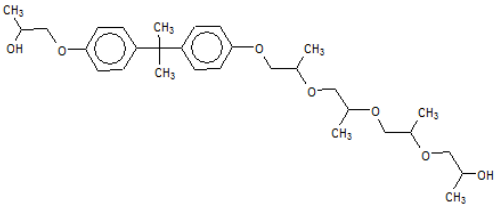
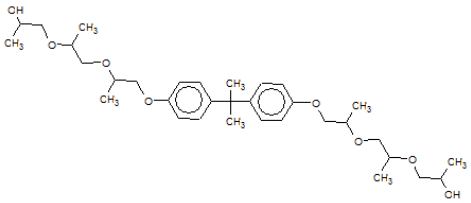
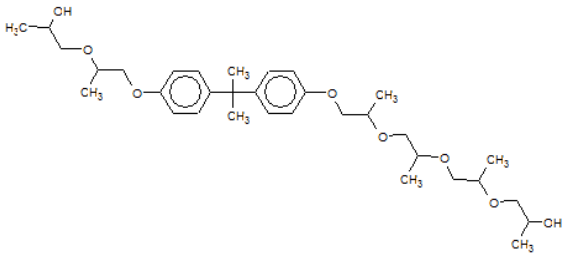
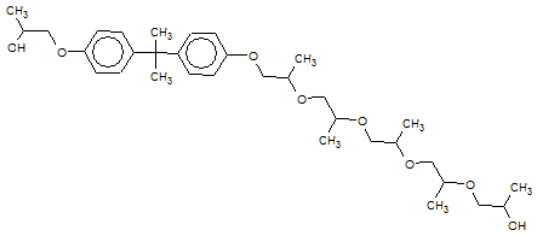
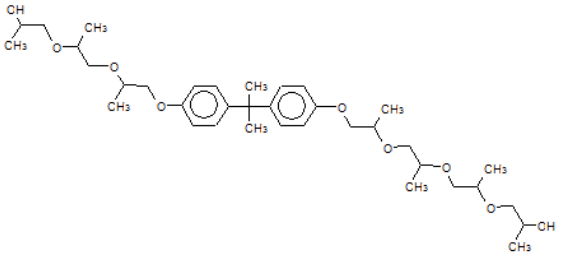
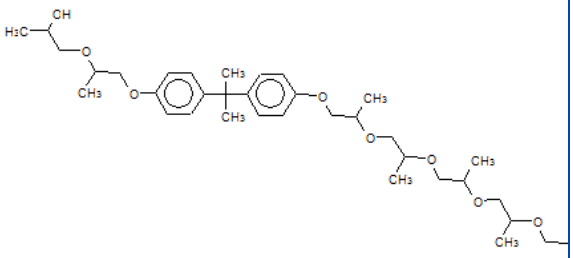
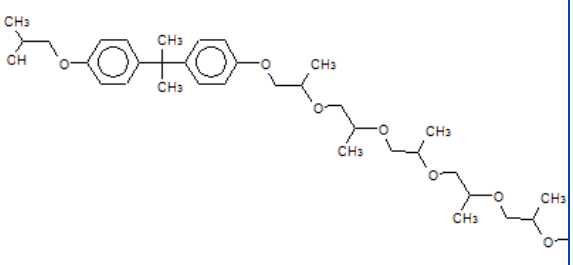
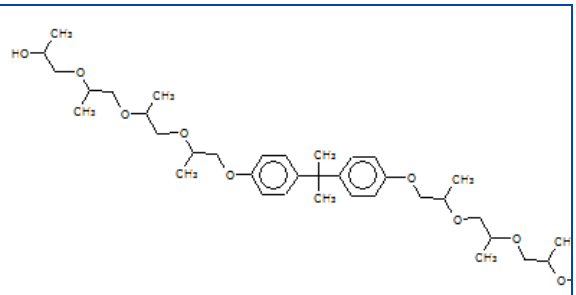
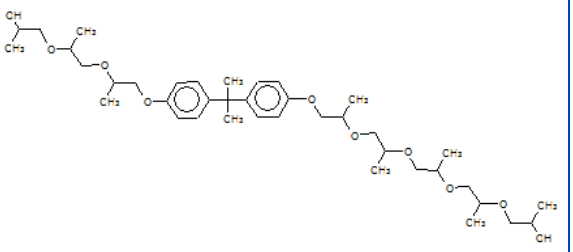
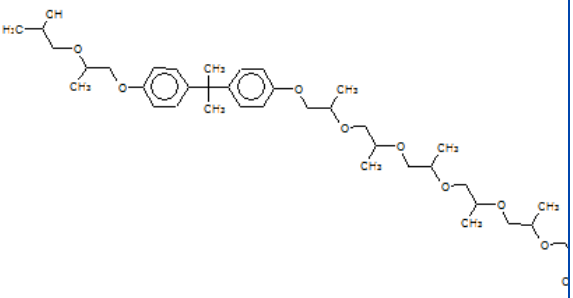
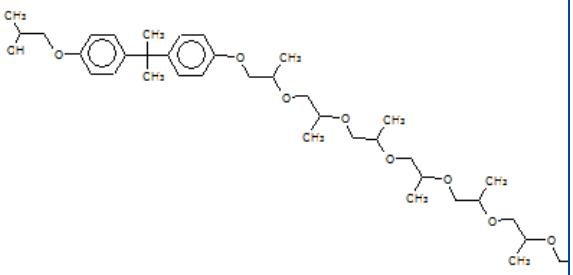
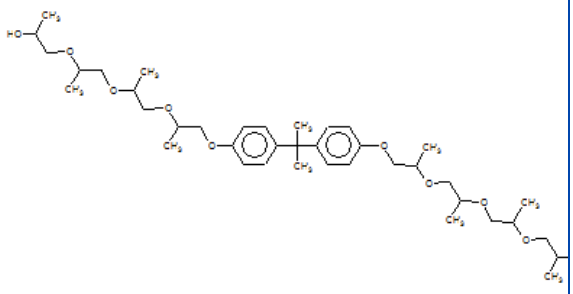
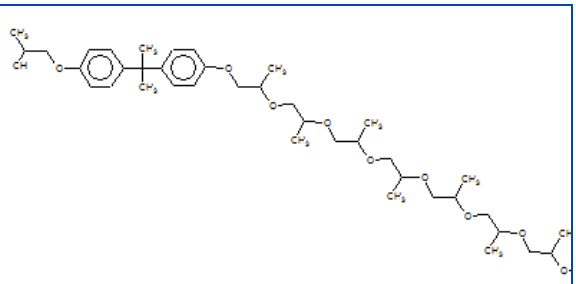
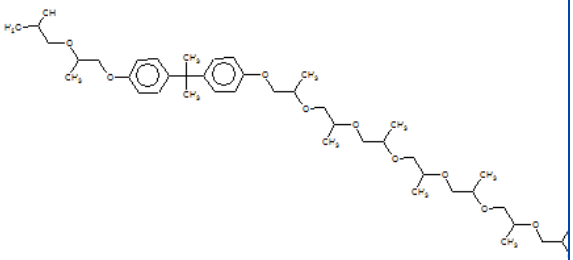
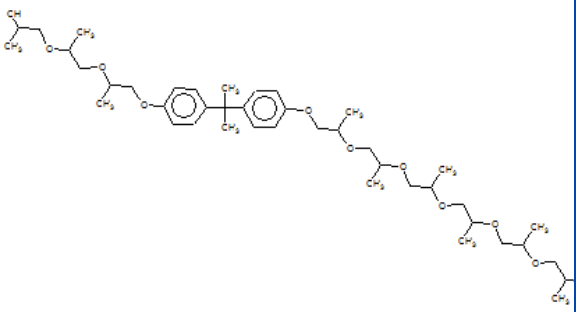
Public Name:	1,1'-isopropylidenebis(p-phenyleneoxy)dipropan-2-ol
EC number:	204-137-9
EC name:	1,1'-isopropylidenebis(p-phenyleneoxy)dipropan-2-ol
CAS number (in the EC inventory):	116-37-0
CAS number:	116-37-0
CAS name:	-
IUPAC name:	1,1'-[propane-2,2-diylbis(4,1-phenyleneoxy)]dipropan-2-ol
Index number in Annex VI of the CLP Regulation	-
Molecular formula:	C21H28O4
Structural formula:	
Molecular weight range:	344 g/mol
Synonyms:	BPA 2PO

Table 6

Constituents		
Constituents	**Smiles**	**Structural formula**
BPA 2PO_1_1	c1(C(c2ccc(OCC(C)O)cc2)(C)C)ccc(OCC(C)O)cc1	
BPA 2PO_0_2	c1(C(c2ccc(O)cc2)(C)C)ccc(OCC(C)OCC(C)O)cc1	
BPA 3PO_1_2	c1(C(c2ccc(OCC(C)OCC(C)O)cc2)(C)C)ccc(OCC(C)O)cc1	
BPA 4PO_2_2	c1(C(c2ccc(OCC(C)OCC(C)O)cc2)(C)C)ccc(OCC(C)OCC(C)O)cc1	
BPA 4PO_1_3	c1(C(c2ccc(OCC(C)O)cc2)(C)C)ccc(OCC(C)OCC(C)OCC(C)O)cc1	
BPA 5PO_2_3	c1(C(c2ccc(OCC(C)OCC(C)O)cc2)(C)C)ccc(OCC(C)OCC(C)OCC(C)O)cc1	
BPA 5PO_1_4	c1(C(c2ccc(OCC(C)O)cc2)(C)C)ccc(OCC(C)OCC(C)OCC(C)OCC(C)O)cc1	

BPA 6PO_3_3	c1(C(c2ccc(OCC(C)OCC(C)OCC(C)O)cc2)(C)C)ccc(OCC(C)OCC(C)OCC(C)O)cc1	
BPA 6PO_2_4	c1(C(c2ccc(OCC(C)OCC(C)O)cc2)(C)C)ccc(OCC(C)OCC(C)OCC(C)OCC(C)O)cc1	
BPA 6PO_1_5	c1(C(c2ccc(OCC(C)O)cc2)(C)C)ccc(OCC(C)OCC(C)OCC(C)OCC(C)OCC(C)O)cc1	
BPA 7PO_3_4	c1(C(c2ccc(OCC(C)OCC(C)OCC(C)O)cc2)(C)C)ccc(OCC(C)OCC(C)OCC(C)OCC(C)OCC(C)O)cc1	
BPA 7PO_2_5	c1(C(c2ccc(OCC(C)OCC(C)O)cc2)(C)C)ccc(OCC(C)OCC(C)OCC(C)OCC(C)OCC(C)O)cc1	
BPA 7PO_1_6	c1(C(c2ccc(OCC(C)O)cc2)(C)C)ccc(OCC(C)OCC(C)OCC(C)OCC(C)OCC(C)OCC(C)O)cc1	

BPA 8PO_4_4	c1(C(c2ccc(OCC(C)OCC(C)OCC(C)OCC(C)O)cc2)(C)C)ccc(OCC(C)OCC(C)OCC(C)OCC(C)O)cc1	
BPA 8PO_3_5	c1(C(c2ccc(OCC(C)OCC(C)OCC(C)O)cc2)(C)C)ccc(OCC(C)OCC(C)OCC(C)OCC(C)O)cc1	
BPA 8PO_2_6	c1(C(c2ccc(OCC(C)OCC(C)O)cc2)(C)C)ccc(OCC(C)OCC(C)OCC(C)OCC(C)OCC(C)O)cc1	
BPA 8PO_1_7	c1(C(c2ccc(OCC(C)O)cc2)(C)C)ccc(OCC(C)OCC(C)OCC(C)OCC(C)OCC(C)OCC(C)O)cc1	
BPA 9PO_4_5	c1(C(c2ccc(OCC(C)OCC(C)OCC(C)OCC(C)O)cc2)(C)C)ccc(OCC(C)OCC(C)OCC(C)OCC(C)OCC(C)O)cc1	

BPA 9PO_1_8	c1(C(c2ccc(OCC(C)O)cc2)(C)C)ccc(OCC(C)OCC(C)OCC(C)OCC(C)OCC(C)OCC(C)OCC(C)O)cc1	
BPA 9PO_2_7	c1(C(c2ccc(OCC(C)OCC(C)O)cc2)(C)C)ccc(OCC(C)OCC(C)OCC(C)OCC(C)OCC(C)OCC(C)O)cc1	
BPA 9PO_3_6	c1(C(c2ccc(OCC(C)OCC(C)OCC(C)O)cc2)(C)C)ccc(OCC(C)OCC(C)OCC(C)OCC(C)OCC(C)OCC(C)O)cc1	

7.4. Physico-chemical properties

Table 7

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	The appearance of the registered substance was recorded as a pale yellow viscous liquid
Vapour pressure	1.8 x 10^-9 Pa at 25°C.
Water solubility	The water solubilities of the three main components of BPA 3PO were reported as 46 mg/l, 11 mg/l and 24 mg/l in the key study.
Partition coefficient n-octanol/water (Log Kow)	The partition coefficients of the three major peaks of the test substance were found to be 2.96 (Peak 1), 3.50 (Peak 2) and 3.62 (Peak 3) in the key study with BPA 3PO.
Flammability	Non flammable

Explosive properties	Non explosive
Oxidising properties	Non oxidising
Granulometry	Not required
Stability in organic solvents and identity of relevant degradation products	The substance is considered to be stable
Dissociation constant	Structural assessment suggests that there will be no dissociation under normal environmental or biological conditions. Under extreme acid or basic conditions, the OH group at the end of each propylene oxide group could in theory dissociate, but the conditions would need to be more extreme than found under normal biological conditions.
Viscosity	Viscosity at 20°C: 20.5 mm^2/s (static)
Autoflammability / self-ignition temperature	400 °C at 1013 hPa
Flash point	The flash point of the test substance was found to be 198°C. The substance is considered to be non-flammable.
Surface tension	The surface activity determined in the key study was 50.4 mN/m. The susbtance does not appear to be surface active i.e. surface tension <60 mN/m
Melting /freezing point	<-20°C at 101.3 kPa
Boiling point	Possible degradation was observed at 350°C and 370°C. The boiling point was reported as >400°C.
Relative density	1.1 at 20°C

The evaluating MSCA has applied QSAR models to investigate the trend in vapour pressure, water solubility and log Kow values for representative structures of constituents in the registered substance BPA PO. The models MPBPWIN (v1.43) (modified Grain method), WATERNT (v.101) and KOWWIN (v1.67) were used. The three models are a part of the EpiSuite programme that can be downloaded from the US EPA website at: http://www.epa.gov/oppt/exposure/pubs/episuite.htm

All constituents were judged to be within the applicability domain of the models. The predicted values are used as supporting information.

Table 8.

OVERVIEW OF PREDICTED PHYSICOCHEMICAL PROPERTIES			
Constituent	**Vapour pressure (Pa) at 25°C (MPBPWIN v1.43)**	**Water solubility (mg/L) (WATERNT v1.01)**	**Partition coefficient n-octanol/water (log value) (KOWWIN v1.67)**
BPA 2PO_0_2	$2.25 \cdot 10^{-8}$	114.57	3.79
BPA 2PO_1_1	$6.78 \cdot 10^{-9}$	3.504	4.06
BPA 3PO_1_2	$1.85 \cdot 10^{-10}$	3.162	4.20
BPA 4PO_2_2	$4.79 \cdot 10^{-12}$	2.795	4.35
BPA 5PO_2_3	$1.47 \cdot 10^{-13}$	2.430	4.49
BPA 6PO_3_3	$4.32 \cdot 10^{-15}$	2.087	4.63
BPA 7PO_3_4	$1.22 \cdot 10^{-16}$	1.774	4.78
BPA 8PO_4_4	$3.31 \cdot 10^{-18}$	1.496	4.92
BPA 9PO_4_5	$8.69 \cdot 10^{-20}$	1.252	5.06
BPA 2PO_1_1	$6.78 \cdot 10^{-9}$	3.504	4.06

7.5. Manufacture and uses

7.5.1. Quantities

Table 9

AGGREGATED TONNAGE (PER YEAR)				
☐ 1 – 10 t	☐ 10 – 100 t	☐ 100 – 1000 t	☒ 1000- 10,000 t	☐ 10,000-50,000 t
☐ 50,000 – 100,000 t	☐ 100,000 – 500,000 t	☐ 500,000 – 1000,000 t	☐ > 1000,000 t	☐ Confidential

7.5.2. Overview of uses

Table 10

USES	Use(s)
Manufacture	Environmental release category ERC1: Manufacture of the substance Process category (PROC): PROC 3: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions PROC 4: Chemical production where opportunity for exposure arises PROC 8a: Transfer of substance or mixture (charging and discharging) at non-dedicated facilities PROC28: Manual maintenance (cleaning and repair) of machinery PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities PROC 9: Transfer of substance or mixture into small containers (dedicated filling line, including weighing) PROC 15: Use as laboratory reagent
Formulation	**Formulation of substance** Environmental release category ERC2: Formulation into mixture PROC 3: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions PROC 4: Chemical production where opportunity for exposure arises PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities PROC 9: Transfer of substance or mixture into small containers (dedicated filling line, including weighing) PROC 15: Use as laboratory reagent Proces category formulated PC 32: Polymer preparations and compounds **Use of polyester resion produced from BPA(PO)n in toner:** ERC2: Formulation into mixture PROC 3: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions PC 18: Ink and toners
Uses at industrial sites	**Industrial use in production of polyester resin** Environmental release category

	ERC6b: Use of reactive processing aid at industrial site (no inclusion into or onto article) Process category PROC 1: Chemical production or refinery in closed process without likelihood of exposure or processes with equivalent containment conditions PROC 2: Chemical production or refinery in closed continuous process with occasional controlled exposure or processes with equivalent containment conditions PROC 3: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions PROC 8a: Transfer of substance or mixture (charging and discharging) at non-dedicated facilities PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities PROC 9: Transfer of substance or mixture into small containers (dedicated filling line, including weighing) PROC 15: Use as laboratory reagent Product category PC 32: Polymer preparations and compounds Sector end use SU 10: Formulation [mixing] of preparations and/or re-packaging (excluding alloys) SU 12: Manufacture of plastics products, including compounding and conversion SU 0: Other: Formulation [mixing] of preparations and/or re-packaging (excluding alloys) **Use in production of resins** ERC6a: Use of intermediate ERC6d: Use of reactive process regulators in polymerisation processes at industrial site (inclusion or not into/onto article) PROC 3: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities PROC 15: Use as laboratory reagent SU 8: Manufacture of bulk, large scale chemicals (including petroleum products) PC 32: Polymer preparations and compounds **Use as monomer** ERC6c: Use of monomer in polymerisation processes at industrial site (inclusion or not into/onto article) PROC 3: Manufacture or formulation in the chemical industry in closed batch processes with occasional controlled exposure or processes with equivalent containment conditions

	PROC 4: Chemical production where opportunity for exposure arises PROC 8b: Transfer of substance or mixture (charging and discharging) at dedicated facilities PROC 9: Transfer of substance or mixture into small containers (dedicated filling line, including weighing) PROC 15: Use as laboratory reagent PC 32: Polymer preparations and compounds
Uses by professional workers	**Use of resin bound toner in copying / printing** ERC11a: Widespread use of articles with low release (indoor) PROC 10: Roller application or brushing PC 18: Ink and toners SU 7: Printing and reproduction of recorded media
Consumer Uses	**Use in toner for printers** ERC8c: Widespread use leading to inclusion into/onto article (indoor) PC 18: Ink and toners
Article service life	**Use of polyester resin produced from BPAPO in toner** AC 02: Other (intended to be released): toner ERC2: Formulation into mixture ERC11a: Widespread use of articles with low release (indoor) PROC 0: Other: toner **Use of resin bound toner in copying / printing** AC 02: Other (intended to be released): toner ERC11a: Widespread use of articles with low release (indoor)

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

Not available

7.6.2. Self-classification

- In the registration(s):

Skin Irrit. 2, H315
Aquatic Chronic 2, H411

- The following hazard classes are in addition notified among the aggregated self-classifications in the C&L Inventory:

Aquatic chronic 3, H412
Skin sens. 1, H317
Eye Irrit. 2, H319

No information has been identified on the diverging classification between notifiers. However, a degree of variation in notified classifications are quite commonly observed for substances in the C&L inventory.

7.7. Environmental fate properties

7.7.1. Degradation

7.7.1.1. Abiotic degradation

7.7.1.1.1. Hydrolysis

Table 11. Studies on hydrolysis

STUDIES ON HYDROLYSIS		
Method	**Results**	**Remarks**
OECD Guideline 111 (Hydrolysis as a Function of pH) EU Method C.7 (Degradation: Abiotic Degradation: Hydrolysis as a Function of pH)	Half-life (DT50): t1/2 (pH 4): > 1 yr at 25 °C; Type: (pseudo-)first order (= DT50) t1/2 (pH 7): > 1 yr at 25 °C; Type: (pseudo-)first order (= DT50) t1/2 (pH 9): > 1 yr at 25 °C; Type: (pseudo-)first order (= DT50)	Klimisch 2 (reliable with restrictions) key study read-across based on grouping of substances (category approach) Test material: BPA 2PO, CAS RN 116-37-0 Form: powder

Evaluating MSCA comment
The study was performed with the structural analogue BPA 2PO. According to our assessment of the registrant(s) read across justification BPA 2PO is not suitable for stand alone read across for some of the applied endpoints (see Annex 2). However, with regard to hydrolysis the read across appears to be valid since the two substances contain the same functional groups (of which none are prone to hydrolysis). Therefore, BPA PO is considered to be hydrolytically stable.

7.7.1.1.2. Phototransformation / photolysis

No relevant information available.

7.7.1.2. Biodegradation

7.7.1.2.1. Biodegradation in water

7.7.1.2.1.1 Screening tests

Table 12. Screening tests for biodegradation in water

SCREENING TESTS FOR BIODEGRADATION IN WATER		
Method	**Results**	**Remarks**
Test type: ready biodegradability activated sludge, domestic (adaptation not specified) OECD Guideline 301 F (Ready Biodegradability: Manometric Respirometry Test)	Not readily biodegradable, inherently biodegradable % Degradation of test substance: ca. 0 after 9 d (O2 consumption) (Lag period) 10 after 12 d (O2 consumption) 35 after 16 d (O2 consumption) 50 after 20 d (O2 consumption) 66 after 28 d (O2 consumption)	Klimisch 2 (reliable with restrictions) key study read-across from supporting substance (structural analogue or surrogate) Test material: BPA 2PO, CAS RN 116-37-0 Form: solid
Test type: ready biodegradability activated sludge, domestic, non-adapted OECD Guideline 301 D (Ready Biodegradability: Closed Bottle Test)	Not readily biodegradable % Degradation of test substance: 0 after 5 d (O2 consumption) 2 after 15 d (O2 consumption) 15 after 28 d (O2 consumption) 29 after 42 d (O2 consumption) 46 after 56 d (O2 consumption) (54% after 70 days and 60% after 98 days)	Klimisch 2 (reliable with restrictions) supporting study read-across from supporting substance (structural analogue or surrogate) Test material: BPA 2PO, CAS RN 116-37-0
Test type: ready biodegradability	readily biodegradable % Degradation of test substance:	Klimisch 4 (not assignable) disregarded study

activated sludge, domestic (adaptation not specified) OECD Guideline 301 B (Ready Biodegradability: CO2 Evolution Test)	101 after 28 d (CO2 evolution) (Values over 100% were attributable to sampling/analytical variation)	Test material: grade BPA 5PO (UVCB) Form: viscous

Evaluating MSCA comment

Two readily biodegradation studies have been performed with the structural analogue BPA 2PO. An OECD TG 301 F (Manometric Respirometry Test) resulted in 66% degradation in 28 days but failed the 10-day window and an OECD TG 301 D (Closed Bottle Test) resulted in 15% degradation in 28 days. The longer chain-length BPA PO derivates in the registered substance are expected to biodegrade at a slower rate than BPA 2PO due to their larger molecular size.

An OECD TG 301 B (CO2 Evolution Test) is available for BPA 5PO (UVCB) and reports 100% biodegradation in 28 days. The study has been given a Klimisch score of 4 in the registration dossier, and has been disregarded for the following reason:

"Although the study was conducted by a GLP accredited lab using OECD Guideline 301B the study is to be disregarded as it has been found to be inconsistent with observations made with similar substances."

The evaluating MSCA agrees with this statement and the conclusion in the registration dossier that BPA PO is to be considered as not readily biodegradable based on the available information.

Since no valid experimental information is available for readily biodegradability on the BPA PO derivatives with longer side chains than BPA 2PO, no conclusion can be drawn on persistency potential of the registered substance. In addition, the evaluating MSCA is of the opinion that there is a data gap with regard to the information requirements of REACH, Annex VII, Section 9.2.1.1 (biodegradation screening test).

As supporting information, QSAR estimates from Biowin have been added by the evaluating MSCA (Table 13) for selected constituents in BPA PO.

Table 13. Predicted biodegradation rate of selected constituents

PREDICTED BIODEGRADATION RATE OF SELECTED CONSTITUENTS				
Constituent	**Compartment**	**Predicted half-life (days) in different media (PBT profiler)**	**BIOWIN (v.4.10)**	**Prediction**
BPA 2PO_1_1	Water Soil Sediment	38 75 **340**	Biowin 2 Biowin 3 Biowin 6	0.958 2.430 **0.339**

BPA 3PO_1_2	Water Soil Sediment	38 75 **340**	Biowin 2 Biowin 3 Biowin 6	**0.245** 2.292 **0.109**
BPA 4PO_2_2	Water Soil Sediment	**60** **120** **540**	Biowin 2 Biowin 3 Biowin 6	**0.005** **2.156** **0.028**
BPA 5PO_2_3	Water Soil Sediment	**60** **120** **540**	Biowin 2 Biowin 3 Biowin 6	**<0.001** **2.019** **0.007**
BPA 6PO_3_3	Water Soil Sediment	**60** **120** **540**	Biowin 2 Biowin 3 Biowin 6	**<0.001** **1.882** **0.002**
BPA 7PO_3_4	Water Soil Sediment	**180** **360** **1,600**	Biowin 2 Biowin 3 Biowin 6	**<0.001** **1.744** **<0.001**
BPA 8PO_4_4	Water Soil Sediment	**180** **360** **1,600**	Biowin 2 Biowin 3 Biowin 6	**<0.001** **1.607** **<0.001**
BPA 9PO_4_5	Water Soil Sediment	180 360 **1,600**	Biowin 2 Biowin 3 Biowin 6	**<0.001** **1.470** **<0.001**

Acoording to REACH, Annex XIII, a substance fulfills the criteria as persistent if at least one of the following conditions is met: a half-life in freshwater of above 40 days, a half-life in freshwater sediment of above 120 days or a half-life in soil of above 120 days. In Table 13, predicted biodegradation rates that are above the cut-off criteria for persistence have been added in bold.

According to the REACH PBT Guidance Document, a substance fulfills the screening criteria for persistency if at least one of the two following combined predictions are achieved in Biowin:

- Biowin 2 gives a probability < 0.5 and Biowin 3 gives a probability < 2.2
- Biowin 6 gives a probability < 0.5 and Biowin 3 gives a probability < 2.2

The lower propoxylated constituents (BPA 2PO and BPA 3PO) are predicted not to meet the screening persistency criterion wereas the higher constituents (BPA 4PO and above) are predicted to be persistent.

7.7.1.2.1.2. Simulation tests (water and sediments)

No information is available and the information requirement in REACH, Annex IX, Section 9.2 regarding biodegradation simulation testing have been waived. The evaluating MSCA has the following two observations:

1. The substance cannot be assumed to be readily biodegradable or to be highly insoluble in water and therefore the adaptation possibility (REACH, Annex IX, Section 9.2.1.2, Column 2) does not apply based on the existing information

2. According to REACH (REACH, Annex IX, Section 9.2, Column 2) further biotic degradation testing does not need to be conducted unless the chemical safety assessment according to Annex I indicates the need to investigate further the degradation of the substance and its degradation products. The evaluating MSCA is of the opinion that the currently available information in the registration dossier is inadequate to determine if this adaptation possibility can be used or not.

7.7.1.2.2. Biodegradation in soil

No information is available.

7.7.1.3. Summary and discussion of degradation

BPA PO is a UVCB composed of BPA constituents with varying chain lengths of propoxylated groups. Valid information on biodegradation is only available for the short chained constituent BPA 2PO. The evaluating MSCA is therefore of the opinion that the standard information requirements of REACH, Annex VII, Section 9.2.1.1 (biodegradation screening test) may not be adequately addressed.

7.7.2. Environmental distribution

7.7.2.1 Adsorption / desorption

The studies on adsorption/desorption are summarised in table 14.

Table 14. Studies on adsorption / desorption

STUDIES ON ADSORPTION / DESORPTION		
Method	**Results**	**Remarks**
Study type: adsorption/desorption (soil/sewage sludge) HPLC estimation method OECD Guideline 121 (Estimation of the Adsorption Coefficient (Koc) on Soil and on Sewage Sludge using	Adsorption coefficient: log Koc: 3.26 at 35 °C (Compound I; peak area = 0.83%) log Koc: 3.35 at 35 °C (Compound II; peak area = 16%)	key study read-across from supporting substance (structural analogue or surrogate) Test material: BPA 2PO

High Performance Liquid Chromatography (HPLC)) EU Method C.19 (Estimation of the Adsorption Coefficient (KOC) on Soil and Sewage Sludge Using High Performance Liquid Chromatography (HPLC))	log Koc: 3.44 at 35 °C (Compound III; peak area = 83%) Koc: 1819 at 35 °C (Compound I; peak area = 0.83%) Koc: 2238 at 35 °C (Compound II; peak area = 16%) Koc: 2754 at 35 °C (Compound III; peak area = 83%)	

The determined K_{oc} values for BPA 2PO indicate that the substance will be immobile in the soil compartment.

The information on adsorption/desorption has not been reviewed by the evaluating MSCA. However, as the study was performed on the constituent BPA 2PO it can be assumed that longer chained BPA PO derivates will have even lower mobility in soil.

7.7.2.2. Volatilisation

No relevant information available.

7.7.2.3. Distribution modelling

Distribution of individual constituents in the environment has been modelled with the Mackay level III steady state fugacity model. Emission rates were set to equal amounts (1,000 kg/hr) to air, soil, and water. The results are presented in Table 15.

Table 15. Modelled distribution of constituents in BPA 2PO to water, soil, sediment and air.

MODELLED DISTRIBUTION OF CONSTITUENTS IN BPA 2PO TO WATER, SEDIMENT AND SOIL				
Constituent	**Water (%)**	**Soil (%)**	**Sediment(%)**	**Air (%)**
BPA 2PO_1_1	14	86	0	0
BPA 3PO_1_2	13	87	1	0
BPA 4PO_2_2	10	90	1	0
BPA 5PO_2_3	9	90	1	0

BPA 6PO_3_3	9	90	1	0
BPA 7PO_3_4	4	95	1	0
BPA 8PO_4_4	4	94	1	0
BPA 9PO_4_5	4	94	2	0

7.7.2.4. Summary and discussion of environmental distribution

Based on Makay level III fugacity modelling, and assuming equal and continuous release to water, soil and air, constituents in BPA PO are predicted to distribute to soil and water with minor distribution to sediment and neglible distribution to air.

7.7.3. Bioaccumulation

7.7.3.1. Aquatic bioaccumulation

No information on aquatic bioaccumulation is available and the standard information requirement of REACH, Annex IX, Section 9.3.2 has been waived by the registrant.

The evaluating MSCA notes that the log Kow that has been seleceted by the registrant only covers the shorter propoxylated BPA PO derivates. Longer propoxylated BPA PO derivates are predicted to have higher log Kow values of which some fullfil the PBT screening criterion of log Kow > 4.5.

Predicted values for BCF and BAF are provided in Table 16 for individual constituents as supporting information.

Table 16. Predicted BCF and biotransformation half-life for constituents

PREDICTED BCF AND BIOTRANSFORMATION HALF-LIFE FOR CONSTITUENTS				
Constituent	**BCF (regression based)**	**BCF (Arnot-Gobas)[1]**	**BCF (Arnot-Gobas)[2]**	**Biotransformation half-life (days)**
BPA 2PO_1_1	123	422	1180	1.54
BPA 3PO_1_2	153	430	1616	1.38
BPA 4PO_2_2	190	422	2201	1.23
BPA 5PO_2_3	236	421	2975	1.15
BPA 6PO_3_3	294	412	3983	1.08

BPA 7PO_3_4	365	398	5265	1.02
BPA 8PO_4_4	454	381	6847	0.96
BPA 9PO_4_5	564	361	8728	0.90

[1]Higher trophic level, including biotransformation rate estimates
[2]Higher trophic level, assuming a biotransformation rate of zero

Some of the bioaccumulation models in the BCFBAF (v3.01) software have been used to predict bioaccumulation potential for selected constituents in BPA PO. The regression based models predict an increasing BCF trend with increasing PO chain length. In contrast, the Arnot-Gobas model predicts a decreasing trend with increasing PO chain length (and log Kow) when bioaccumulation rate estimates are included in the model. The Arnot-Gobas BCF values that have been predicted when assuming a biotransformation rate of zero are considerably higher than other model estimates. However, the scenario of zero biotransformation is not very realistic.

The evaluating MSCA is of the opinion that the currently available information is insufficient to conclude on the bioaccumulation potential of BPA PO. Some of the constituents may have BCF values that exceed the CLP classification cut-off value of 500. In addition, although considered as unlikely, it cannot be excluded that some of the longer PO derivates may exceed the bioaccumulation criterion of BCF = 2000.

7.7.3.2. Terrestrial bioaccumulation

No relevant information available

7.7.3.3. Summary and discussion of bioaccumulation

The evaluating MSCA is of the opinion that the standard information requirements of REACH, Annex IX, Section 9.3.2 may not be adequately addressed.

7.7.4. Secondary poisoning

An assessment of secondary poisoning has not been performed. The evaluating MSCA notes that in order to decide for the need for such an assessment robust bioaccumulation information is needed, which is not present in the registration dossier. In addition toxicity data for mammals is needed to make such an assessment. However, presently only screening/short term studies are available.

7.8. Environmental hazard assessment

7.8.1. Aquatic compartment (including sediment)

7.8.1.1. Fish

7.8.1.1.1. Short-term toxicity to fish

The results are summarised in table 17.

Table 17. Short-term effects on fish

SHORT-TERM EFFECTS ON FISH		
Method	**Results**	**Remarks**
Cyprinus carpio freshwater static OECD Guideline 203 (Fish, Acute Toxicity Test) EU Method C.1 (Acute Toxicity for Fish) ISO 7346-1 (Determination of the Acute Lethal Toxicity of Substances to a Freshwater Fish [Brachydanio rerio Hamilton-Buchanan (Teleostei, Cyprinidae)] - Part 1: Static Method)	LC50 (2.5 h): 21 mg/L test mat. (meas. (initial)) based on: mortality (16-28) LC50 (24 h): 13 mg/L test mat. (meas. (initial)) based on: mortality (11-16) LC50 (48 h): 12 mg/L test mat. (meas. (initial)) based on: mortality (8.3-16) LC50 (72 h): 9.1 mg/L test mat. (meas. (initial)) based on: mortality (estimated) LC50 (96 h): 8.8 mg/L test mat. (meas. (initial)) based on: mortality (estimated)	Klimisch 2 (reliable with restrictions) key study read-across from supporting substance (structural analogue or surrogate) **Test material: BPA 2PO** Form: powder
Oncorhynchus mykiss freshwater semi-static OECD Guideline 203 (Fish, Acute Toxicity Test)	LC50 (96 h): 8.8 mg/L test mat. (nominal) based on: mortality (and sub-lethal effects) (95% CL = 6.4-12 mg/L) LC50 (96 h): 11 mg/L test mat. (meas. (initial)) based on: mortality (and sub-lethal effects) (95% CL = 7.8-15 mg/L)	Klimisch 1 (reliable without restriction) supporting study experimental result **Test material: BPA 5PO (UVCB)** Form: viscous

Evaluating MSCA comment

The information is reported as presented by the Registrant(s) and has not been reviewed by the evaluating MSCA.

7.8.1.1.2. Long-term toxicity to fish

No relevant information is available.

7.8.1.2. Aquatic invertebrates

7.8.1.2.1. Short-term toxicity to aquatic invertebrates

The results are summarised in table 18

Table 18. Short-term effects on aquatic invertebrates

SHORT-TERM EFFECTS ON AQUATIC INVERTEBRATES		
Method	**Results**	**Remarks**
Daphnia magna freshwater static OECD Guideline 202 (Daphnia sp. Acute Immobilisation Test) EU Method C.2 (Acute Toxicity for Daphnia) ISO 6341 15 (Water quality - Determination of the Inhibition of the Mobility of Daphnia magna Straus (Cladocera, Crustacea))	EC50 (24 h): 16 mg/L test mat. (meas. (initial)) based on: mobility (13-22) EC50 (48 h): 2.3 mg/L test mat. (meas. (initial)) based on: mobility (1.7-3.1)	Klimisch 1 (reliable without restriction) key study read-across based on grouping of substances (category approach) **Test material: BPA 2PO** Form: powder
Daphnia magna freshwater static OECD Guideline 202 (Daphnia sp. Acute Immobilisation Test)	EC50 (48 h): 32 mg/L test mat. (nominal) based on: Immobilisation and any other adverse reactions (95% CL = 22-50 mg/L)	Klimisch 1 (reliable without restriction) supporting study experimental result **Test material: BPA 5PO (UVCB)** Form: viscous

Evaluating MSCA comment

The information is reported as presented by the Registrant(s) and has not been reviewed by the evaluating MSCA.

7.8.1.2.2. Long-term toxicity to aquatic invertebrates

No relevant information is available.

7.8.1.3. Algae and aquatic plants

The results are summarised in table 19.

Table 19. Effects on algae and aquatic plants

EFFECTS ON ALGAE AND AQUATIC PLANTS		
Method	**Results**	**Remarks**
Pseudokirchnerella subcapitata (algae) freshwater static OECD Guideline 201 (Alga, Growth Inhibition Test) EU Method C.3 (Algal Inhibition test) ISO 8692 (Water Quality - Fresh Water Algal Growth Inhibition Test with Scenedesmus subspicatus and Selenastrum capricornutum)	EC50 (72 h): 28 mg/L test mat. (meas. (initial)) based on: growth rate (11-71) EC50 (72 h): 8.5 mg/L test mat. (meas. (initial)) based on: yield (5.3-14) NOEC (72 h): 2.5 mg/L test mat. (meas. (initial)) based on: growth rate (.) NOEC (72 h): 2.5 mg/L test mat. (meas. (initial)) based on: yield (.) EC10 (72 h): 5.1 mg/L test mat. (meas. (initial)) based on: growth rate (2.0-13) EC10 (72 h): 2.8 mg/L test mat. (meas. (initial)) based on: yield (1.7-4.6)	Klimisch 2 (reliable with restrictions) key study read-across from supporting substance (structural analogue or surrogate) **Test material: BPA 2PO** Form: powder
Desmodesmus subspicatus (algae) freshwater static OECD Guideline 201 (Alga, Growth Inhibition Test)	EC50 (72 h): 49 mg/L test mat. based on: growth rate EC50 (72 h): 22 mg/L test mat. based on: yield	Klimisch 1 (reliable without restriction) supporting study experimental result **Test material: BPA 5PO (UVCB)** Form: viscous

Evaluating MSCA comment

The information is reported as presented by the Registrant(s) and has not been reviewed by the evaluating MSCA.

7.8.1.4. Sediment organisms

No relevant information is available.

7.8.1.5. Other aquatic organisms

No relevant information is available.

7.8.2. Terrestrial compartment

No relevant information is available.

7.8.3. Microbiological activity in sewage treatment systems

The results are summarised in table 20.

Table 20. Effects on micro-organisms

EFFECTS ON MICRO-ORGANISMS		
Method	**Results**	**Remarks**
activated sludge of a predominantly domestic sewage freshwater static OECD Guideline 209 (Activated Sludge, Respiration Inhibition Test) EU Method C.11 (Biodegradation: Activated Sludge Respiration Inhibition Test) ISO 8192 (Test for Inhibition of Oxygen Consumption by Activated Sludge)	NOEC (3 h): 100 mg/L test mat. (nominal) based on: respiration rate (loading rate) EC50 (3 h): > 100 mg/L test mat. (nominal) based on: respiration rate (loading rate)	Klimisch 2 (reliable with restrictions) key study read-across from supporting substance (structural analogue or surrogate) **Test material: BPA 2PO** Form: powder
activated sludge of a predominantly domestic sewage freshwater static	EC50 (3 h): > 1000 mg/L test mat. based on: respiration rate	Klimisch 1 (reliable without restriction) supporting study experimental result

EU Method C.11 (Biodegradation: Activated Sludge Respiration Inhibition Test)		**Test material: BPA 5PO (UVCB)** Form: viscous
activated sludge of a predominantly domestic sewage freshwater static EU Method C.11 (Biodegradation: Activated Sludge Respiration Inhibition Test)	EC50 (3 h): > 1000 mg/L test mat. based on: respiration rate	Klimisch 2 (reliable with restrictions) supporting study read-across from supporting substance (structural analogue or surrogate) **Test material: BPA 2PO**

Evaluating MSCA comment

The information is reported as presented by the Registrant(s) and have not been reviewed by the evaluating MSCA.

7.8.4. PNEC derivation and other hazard conclusions

Not reviewed.

7.8.5. Conclusions for classification and labelling

Not reviewed.

7.9. Human Health hazard assessment

7.9.1. Toxicokinetics

7.9.1.1. Non-human information

Very limited information is available. Since effects are observed in the oral repeated dose study it can be assumed that the substance is absorbed and distributed after oral exposure.

7.9.1.2. Human information

No relevant information available.

7.9.1.3. Summary and discussion of toxicokinetics

It can be assumed that the substance is absorbed and distributed after oral exposure.

7.9.2. Acute toxicity and Corrosion / Irritation

7.9.2.1. Acute toxicity

7.9.2.1.1 Non-human information

7.9.2.1.1.1 Acute toxicity: oral

The results of studies on acute toxicity after oral administration are summarised in Table 21.

Table 21.

STUDIES ON ACUTE TOXICITY AFTER ORAL ADMINISTRATION		
Method	**Results**	**Remarks**
rat (Sprague-Dawley) male/female oral: gavage OECD Guideline 401 (Acute Oral Toxicity)	LD50: > 2000 mg/kg bw (male/female) based on: test mat.	Klimisch 2 (reliable with restrictions) key study read-across from supporting substance (structural analogue or surrogate) **Test material BPA 2PO** Form: viscous
rat (Crj: CD(SD)) female oral: gavage OECD Guideline 423 (Acute Oral toxicity - Acute Toxic Class Method)	LD50: > 2000 mg/kg bw (female)	Klimisch 1 (reliable without restriction) supporting study experimental result **Test material: grade BPA 5PO (UVCB)** Form: viscous
rat (Sprague-Dawley) male/female intubation The test was carried out by means of stomach intubation in rats that had been fasted. Food was given after the dose was received.	LD50: 3.65 g/kg bodyweight (male) (Using method of Weil 1952) LD50: 3.42 g/kg bodyweight (male) (Using method of Litchfield and Wilcoxon 1949) LD50: 2.81 g/kg bodyweight (female)	Klimisch 2 (reliable with restrictions) supporting study read-across from supporting substance (structural analogue or surrogate) **Test material BPA 2PO** experimental result

	(Using method of Weil 1952) LD50: 3.03 g/kg bodyweight (female) (Using method of Litchfield and Wilcoxon 1949) LD50: 3.27 g/kg bodyweight (male/female) (Using method of Weil 1952) LD50: 3.23 g/kg bodyweight (male/female) (Using method of Litchfield and Wilcoxon 1949)	Form: viscous

Evaluating MSCA comment

The information is reported as presented by the Registrant(s) and has not been reviewed by the evaluating MSCA.

7.9.2.1.1.2. Acute toxicity: inhalation

No information is available.

7.9.2.1.1.3. Acute toxicity: dermal

The results of studies on acute toxicity after dermal administration are summarised in Table 22.

Table 22.

STUDIES ON ACUTE TOXICITY AFTER ORAL ADMINISTRATION		
Method	**Results**	**Remarks**
rat (Sprague-Dawley) male/female Coverage: occlusive Vehicle: water EU Method B.3 (Acute Toxicity (Dermal))	LD50: > 2000 mg/kg bw (male/female) based on: test mat.	Klimisch 1 (reliable without restriction) key study experimental result **Test material: grade BPA 5PO (UVCB)** Form: viscous

Evaluating MSCA comment

The information is reported as presented by the Registrant(s) and has not been reviewed by the evaluating MSCA.

7.9.2.1.1.4. Acute toxicity: other routes

No relevant information available.

7.9.2.1.2. Human information

No relevant information available.

7.9.2.1.3. Summary and discussion of acute toxicity

Not evaluated.

7.9.2.2. Irritation

7.9.2.2.1. Skin

7.9.2.2.1.1. Non-human information

The results of studies on skin irritation are summarised in table 23.

Table 23.

STUDIES ON SKIN IRRITATION		
Method	**Results**	**Remarks**
in vitro study human (Three dimensional human skin model) Coverage: In vitro Vehicle: unchanged (no vehicle) OECD Guideline for the testing of chemicals, Draft proposal for a new guideline: In Vitro Skin Irritation: Human Skin Model Test, December 2009. (Revision of OECD Guideline 404 Acute Dermal Irritation).	irritating Tissue viability as percentage of optical density negative control: 14.3 (mean) (+/- 2.7 %)	Klimisch 1 (reliable without restriction) key study experimental result **Test material grade BPA 3PO (UVCB)** Form: viscous
rabbit (New Zealand White)	not irritating	Klimisch 2 (reliable with restrictions)

Coverage: occlusive (three abraded and three intact, each on a different rabbit) Appraisal of the Safety of Chemicals in Food, Drugs and Cosmetics. Association of Food and Drug Officials, US, 1959.	Primary dermal irritation index (PDII): 0 (mean) (For intact treated skin) Primary dermal irritation index (PDII): 0 (mean) (For abraded treated skin)	key study read-across from supporting substance (structural analogue or surrogate) **Test material** Inconsistent substance ID information reported in the registration dossier. Form: viscous
rabbit (New Zealand White) Coverage: semiocclusive (clipped) OECD Guideline 404 (Acute Dermal Irritation / Corrosion)	mild irritant Primary dermal irritation index (PDII): 1 (mean)	Klimisch 1 (reliable without restriction) supporting study read-across from supporting substance (structural analogue or surrogate) **Test material** Inconsistent substance ID information reported in the registration dossier. Form: viscous

Evaluating MSCA comment

The information is reported as presented by the Registrant(s) and has not been reviewed by the evaluating MSCA. However, it is noted that inconsistent information is given on the identity of the tested substance in the two *in vivo* skin irritation studies. This should be clarified/corrected by the Registrant(s).

7.9.2.2.1.2. Human information

No relevant information available

7.9.2.2.2. Eye

7.9.2.2.2.1. Non-human information

The results of studies on eye irritation are summarised in table 24.

Table 24.

STUDIES ON EYE IRRITATION

Method	Results	Remarks
bovine Vehicle: unchanged (no vehicle) OECD Test Guideline 437 Bovine Corneal Opacity and Permeability Test Method for Identifying Ocular Corrosives and Severe Irritants	not irritating Overall irritation score: -1 (mean) (Score is +/- 1.2 (Standard Deviation)) : -1.3 (mean) (Score is +/- 1 (Standard Deviation)) : 0.02 (mean) (Score is +/- 0.015 (Standard Deviation))	Klimisch 1 (reliable without restriction) key study experimental result **Test material grade BPA 3PO (UVCB)** Form: viscous

Evaluating MSCA comment

The information is reported as presented by the Registrant(s) and has not been reviewed by the evaluating MSCA.

7.9.2.3. Corrosivity

Not reviewed.

7.9.3. Sensitisation

7.9.3.1. Skin

7.9.3.1.1. Non-human information

The results of studies on skin sensitisation are summarised in Table 25.

Table 25.

STUDIES ON SKIN SENSITIZATION		
Method	**Results**	**Remarks**
mouse (CBA) female Local lymph node assay OECD Guideline 429 (Skin Sensitisation: Local Lymph Node Assay)	not sensitising Stimulation index: Dpm for test/Dpm for control ratio. Ratio of more than 3 indicates a positive response.	Klimisch 1 (reliable without restriction) key study experimental result **Test material grade BPA 3PO (UVCB)** Form: viscous

Evaluating MSCA comment

The information is reported as presented by the Registrant(s) and has not been reviewed by the evaluating MSCA.

7.9.3.2. Respiratory system

No relevant information available.

7.9.3.3 Summary and discussion of sensitisation

Not reviewed.

7.9.4. Repeated dose toxicity

7.9.4.1. Non-human information

7.9.4.1.1. Repeated dose toxicity: oral

The results of studies on repeated dose toxicity after oral administration are summarised in Table 26.

Table 26.

STUDIES ON REPEATED DOSE TOXICITY AFTER ORAL ADMINISTRATION		
Method	**Results**	**Remarks**
Rat (Sprague-Dawley) male/female sub-chronic toxicity: oral gavage 0mg/kg bw/day 30mg/kg bw/day 120mg/kg bw/day 500mg/kg bw/day Vehicle: olive oil Exposure: 13 weeks followed by a 4-week treatment-free period (daily) according to OECD Test Guideline 408 (Repeated Dose 90-Day Oral Toxicity in Rodents)	NOAEL: 120 mg/kg bw/day (**male**) based on clinical signs; mortality; body weight and weight gain; food consumption and compound intake; haematology; clinical biochemistry; organ weights and organ/ body weight ratios; gross pathology; histopathology: non-neoplastic. NOAEL: 500 mg/kg bw/day (actual dose received) **(female)** based on: not determinable due to absence of adverse toxic effects) **Target system / organ toxicity** Lowest effective dose /concentration: urinary, hepatobiliary and gastrointestinal tract: stomach; liver; bladder (lowest effective dose/conc.: 500 mg/kg bw/day (actual dose received); treatment-related; dose-response:	Klimisch 1 (reliable without restriction) key study experimental study **Test material** 4,4'-Isopropylidenediphenol, propoxylated / CAS 37353-75-6 / Sample 3 **BPA 4PO** Form: liquid **Reference** Unpublished study report, 2018a

	yes).	
Rat (Crl:WI(Han)) male/female combined repeated dose and reproduction / developmental screening (oral: gavage) 0, 125, 250, 500 mg/kg/day (actual ingested) Vehicle: polyethylene glycol (specific gravity 1.125) Exposure: Males were exposed for 29 days, i.e. 2 weeks prior to mating, during mating, and up to the day prior to scheduled necropsy. Females were exposed for 43-54 days, i.e. during 2 weeks prior to mating, during mating, during post-coitum, and during at least 4 days of lactation (up to the day prior to scheduled necropsy). Once daily for 7 days per week, approximately the same time each day with a maximum of 6 hours difference between the earliest and latest dose. Animals were dosed up to the day prior to scheduled necropsy. OECD Test Guideline 422 (Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test)	NOAEL (Parental generation): 125 mg/kg bw/day (actual dose received) (male/female) based on: test mat. (Toxicologically relevant effects on mortality, clinical signs, body weight, food consumption, food efficiency, gross pathology, organ weights and histopathology at 250 and 500 mg/kg.)	Klimisch 2 (reliable with restrictions) supporting study read-across from supporting substance (structural analogue or surrogate) **Test material** **BPA 2PO** Form: powder **Reference** Unpublished study report, 2011
rat (Crj: CD(SD)) male/female combined repeated dose and reproduction / developmental screening (oral: gavage) 0 mg/kg 30 mg/kg 120 mg/kg 500 mg/kg Vehicle: olive oil	NOAEL: 500 mg/kg bw/day (nominal) (male/female) based on: test mat. (Clinical chemistry changes and adaptive liver changes at 500 mg/kg/day. Not necessarily 'adverse' effects.) NOEL: 30 mg/kg bw/day (nominal) (male/female) based on: test mat. (Adaptive clinical chemistry and liver	Klimisch 1 (reliable without restriction) supporting study experimental result **Test material** **grade BPA 5PO (UVCB)** Form: liquid, viscous **Reference** Ministry of Health, Labour and Welfare, Japan, 2010

Exposure: 42 days (Daily) equivalent or similar to OECD Test Guideline 422 (Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test)	changes 500 mg/kg/day)	

Sub-chronic repeated-dose toxicity

Investigation of the sub-chronic (90-day) repeated-dose toxicity of the registered substance was performed as requested in the ECHA Decision.
A concern for systemic toxicity was identified in the OECD 422 study conducted with Grade 5 of BPA PO based on dilatation of lacteals, effects on the small intestine, and high rate of oestrus cycle disorder. This test substance was therefore considered as more relevant than BPA 2PO for subsequent repeated-dose toxicity testing.

However, Grade 5 of BPA PO is regarded as a polymer under REACH, so it was a ruled out as a test substance for the purpose of the sub chronic repeated-dose toxicity testing. The outcome of the Combined Repeated Dose Toxicity Study with the Reproduction/ Developmental Toxicity Screening studies suggested that potential endocrine disruption properties could be related to a higher degree of propoxylation and constituents with higher chain-length. Therefore, Grade 4 of BPA PO was deemed as the most relevant test substance for this study. The study was performed according to the 1998 version of OECD TG 408, i.e. before the 2018 update where a number of endocrine-related measurements, particularly relevant to thyroid function were added. The objective of this study was to evaluate the potential toxicity of the test item following daily oral administration (gavage) to rats for 13 weeks. On completion of the treatment period, designated animals were held for a 4-week treatment-free period in order to evaluate the reversibility of the findings.

Two groups of 10 male and 10 female (low- and mid-doses) and one group of 15 male and 15 female (high-dose) Sprague-Dawley rats were treated daily by the oral route (gavage) with the test item, at dose-levels of 30, 120 or 500 mg/kg bw/d for 13 weeks. The test item was administered as an emulsion in the vehicle (olive oil) under a constant dosage-volume of 5 mL/kg/day.
Another group of 15 male and 15 female Sprague-Dawley rats received the vehicle alone under the same experimental conditions and acted as a control group. The actual test item concentrations in the dose formulations prepared for use in Weeks 1, 4, 8 and 12 were determined using a HPLC with UV detection analytical method. The animals were observed daily for mortality and clinical signs. Detailed clinical examinations were performed weekly and a Functional Observation Battery (FOB) was conducted in Week 12. Body weight was recorded once pre-test, on the first day of treatment and then at least once a week. Food consumption was recorded once a week.
Ophthalmology examinations were performed pre-test on all animals and at the end of the treatment period on all control- and high-dose animals. Haematology and blood biochemistry investigations were performed at the end of the treatment and treatment-free periods. On completion of the treatment or treatment-free periods, the animals were sacrificed and a full macroscopic post-mortem examination was performed. Designated organs were weighed (adrenals, epididymis, liver, kidney, spleen, thymus, testes, ovary and uterus) and selected tissue specimens were preserved. Weights of pituitary, prostate and thyroid gland, which were significantly affected in the TG 443 study (see 7.9.7), were not obtained in the present study. A microscopic examination was performed on selected tissues for the control- and high-dose animals sacrificed at the end of the treatment period. A microscopic examination was also performed on selected tissues

for the low- and intermediate-dose animals sacrificed at the end of the treatment period and for the control- and high-dose animals sacrificed at the end of the treatment-free period.

At 500 mg/kg bw/d, the test item induced adverse effects in males on the clinical condition, body weight and food consumption leading to premature sacrifice (during the last 2 weeks of the treatment period) of five males, for ethical reasons. In males receiving 500 mg/kg bw/d, significantly lower body weight gain and body weights, were noted from the beginning until the end of the treatment period. The decrease was marked, with a 20% lower mean body weight on day 91, and a 34% decrease in weight gain over the 13-week test period. In large contrast to the effects in the males, statistically significantly higher mean body weight were observed in females receiving 500 mg/kg bw/day. The effects were seen from the beginning until the end of the treatment period, with a body weight on day 91 which was 9% higher than in control animals and a body weight increase over the study period which was 18% higher than in control females.
Slight to moderate changes in clinical pathology were noted in both sexes. There were markedly higher liver weights in males and females that correlated with gross enlargement and microscopic hepatocellular hypertrophy, higher adrenal gland weights in males and females, correlated with the microscopic vacuolation of the adrenal cortex, higher kidney weights in females and decreased thymus weights in males correlated with the lymphoid atrophy. At gross examination, there were test item-related enlarged liver in 6/7 males that correlated with the hepatocellular hypertrophy. The black discoloration and the red discoloration correlated with microscopic centrilobular degeneration/necrosis and haemorrhage, respectively. The small seminal vesicles seen in 1/7 males correlated with acinar cell atrophy and decreased secretory content while the thickening the stomach from in 2/7 males treated at 500 mg/kg bw/d correlated with the mineralization and increased regeneration in the gland. At microscopic examination, there were adverse findings in the liver, urinary bladder and stomach from males treated at 500 mg/kg bw/d and non-adverse findings in the pituitary gland, mandibular lymph nodes, mesenteric lymph nodes, mesenteric artery, thyroid glands, parathyroid, heart, lungs, adrenals, kidneys, jejunum, GALT (Gut-associated lymphoid tissue), prostate and seminal vesicles, sternum, bone marrow, ovaries, vagina and thymus in males and/or, to a lesser extent, in females treated at 500 mg/kg bw/d. At the end of the treatment-free period, there were kidney and adrenal weight differences while there were no thymus or liver weights differences considered to be related to the test item administration. There were no test item-related gross findings while there were microscopic non-adverse findings in the liver (in males only), mesenteric lymph nodes, mesenteric artery, thyroid glands, heart (in males only), adrenals (in females only), kidneys, jejunum, sternum, bone marrow, and ovaries. These observations were considered non-adverse and suggested an incomplete reversibility of test item-related changes.

At 120 mg/kg bw/d, the test item induced lower body weight and food consumption in males and slight changes in blood biochemistry parameters in both sexes. There were non-adverse findings in the liver, adrenals, kidneys, jejunum, GALT, prostate and seminal vesicles and sternum.
At 30 mg/kg bw/d, the test item induced lower body weight in males and slight increase in cholesterol level in both sexes. There were non-adverse findings in the liver, prostate and seminal vesicles.

The results from the cholesterol level analyses were shown in the study report (Unpublished study report, 2018a), but in spite of very marked effects, these results were not highlighted or discussed in any way in this study report. The study showed statistically significant increases in total cholesterol levels in BPA 4PO exposed animals of both sexes at all the tested dose levels. In males the increases in the three dose groups were +17%, +54% and +280% respectively, and in females the increases were +22%, +32% and +195% respectively. These changes were no longer statistically significant at the end of the treatment-free period. However, in females from the high dose group a non-significant 25% increase in cholesterol was still observed. This indicates that the

cholesterol increases might to some extent still be present, even after a 4 week exposure free period. In the study report, it was stated that all blood biochemistry changes were considered test item related, with a clear dose-relationship. However, no discussion or conclusion regarding adversity or toxicological relevance was included in the study report.

Under the experimental conditions of the study, based on adverse effect observed at 500 mg/kg bw/d in males, the No Observed Adverse Effect Level (NOAEL) after the 90-day treatment period was in the study report (Unpublished study report, 2018a) and in the updated CSR (2018), established at 120 mg/kg bw/d in males and at 500 mg/kg bw/d in female.

As discussed in more detail later (section 7.9.4.3) the eMSCA finds that the marked cholesterol increases (especially in the high dose animals) deserve some discussion, and that ignoring the cholesterol effects in the lower dose groups when setting the NOAEL may be incorrect.

Short-term repeated-dose toxicity

Short-term (28-day) repeated-dose toxicity was performed as part of studies conducted in accordance with the OECD Testing Guideline 422 on BPA 2PO and Grade 5 of the registered substance.

Short-term repeated-dose toxicity study conducted on BPA 2PO

The test substance was administered by daily oral gavage to male and female Wistar Han rats at dose levels of 125, 250 and 500 mg/kg bw/day. Males were exposed for 2 weeks prior to mating, during mating, and up to termination (for 29 days). The females were exposed for 2 weeks prior to mating, during mating, during post-coitum, and at least 4 days of lactation (for 43-54 days). Formulation analysis showed that the formulations were prepared accurately, were homogenous, and were stable for at least 6 hours at room temperature.

Treatment related toxicity was evident at 250 and 500 mg/kg bw/day including mortality (3 animals at 250 mg/kg bw/day and 10 animals at 500 mg/kg bw/day), clinical signs (hunched posture, salivation, piloerection and lethargy, among others), changes in body weights, food consumption, haematology and clinical biochemistry parameters, and organ weight and organ to body weight ratios. Unlike the effects of BPA 4PO, the adverse effects (including mortality), were almost equally seen in male and female rats. Macroscopic and microscopic findings in the heart, stomach, brain, pituitary gland, kidneys, liver thymus, skeletal muscle, prostate gland, seminal vesicles, coagulation gland and ovaries were also noted. Additionally, impaired spermatogenesis were noted for males at 250 and 500 mg/kg bw/d.

The study report concluded that no toxicologically significant changes were noted in functional observations, and no toxicologically relevant effects were seen in any parameter at 125 mg/kg bw/day. The eMSCA would however like to stress that a statistically significant, 43% increase in cholesterol levels was seen in males from the low dose (125 mg/kg bw/day) group. The cholesterol increases in the higher dose group males (250 and 500 mg/kg bw/day) were 75% and 140% respectively. In females, the increases in the two highest dose groups were 52% and 173% respectively, whereas the 22% increase in the lowest dose group was not statistically significant. The study report concluded that based on the absence of any treatment related microscopic findings at 125 mg/kg bw/day, the changes in cholesterol were not considered toxicologically relevant. The eMSCA however finds that given the consistency of dose-dependent cholesterol increases in different studies, this conclusion may be incorrect.

In conclusion, treatment with BPA 2PO by oral gavage in male and female Wistar Han rats at dose levels of 125, 250 and 500 mg/kg bw/day revealed parental toxicity at 250 and 500 mg/kg bw/day. This indicates, that in contrast to BPA 4PO, BPA 2PO causes systemic toxicity to a similar degree in both sexes, and that the adverse effects (especially in females) occur at a lower dose than with BPA 4PO.

Short-term toxicity study conducted on Grade 5 of BPA PO
It should be noted that the original study report is in Japanese, with only tables and figures in English. Consequently, some relevant information in the study report may have been missed. The test substance was administered by daily oral gavage to male and female Sprague-Dawley rats at dose levels of 30, 120 and 500 mg/kg bw/day. Males were exposed for 42 days. The females were exposed for 2 weeks prior to mating, during mating, during post-coitum, and at least 4 days of lactation (for 42-53 days). Each group consisted of 12 animals per sex. Five of the 12 male rats were selected from control and 500 mg/kg bw/day group to investigate the recovery for 14 days after dosing. For females, the satellite group consisted of five non-pregnant rats (from control and 500 mg/kg bw/day) to observe recovery.

Body weight in parental (male and female) animals were unaffected by treatment. In the P males, a reduced weight gain was seen in the 500 mg/kg bw/day-group. No effect on the P female weight gain was seen in any of the dose groups during premating, pregnancy or the lactation period. In the non-mated females in the recovery group an overall reduced weight gain and a lower weight was seen in the recovery period. One female rat at 500 mg/kg bw/d died on day 39 (day 22 of pregnancy). Transient salivation was observed at 120 and 500 mg/kg bw/d for both sexes. Emaciation was observed for both sexes at 500 mg/kg bw/d. Incidence of ptosis, decrease in locomotor activity and decrease in body weight gain was observed for males at 500 mg/kg bw/d. Some haematological changes observed at 500 mg/kg bw/d in males as well as in the 500 mg/kg bw/d male and female satellite groups. Neutrophil count was significantly lower in males from the high-dose group at the end of recovery period compared to control. Significant decrease in total protein was observed in male animals at 500 mg/kg bw/d, along with a significant decrease in albumin and significant increase in total cholesterol for both sexes. The cholesterol increases in the high dose group males and females were 82% and 47% respectively. During the urinalysis significantly higher levels of potassium levels in males from the high-dose group on week 2 of the recovery period. Absolute and relative weight of liver increased significantly for males at 500 mg/kg bw/d and relative weight increased for females at 500 mg/kg bw/d. Dilatation of lacteal in small intestine was observed at 500 mg/kg bw/d for both sexes. Hypertrophy of centrilobular hepatocyte was observed at 500 mg/kg bw/d for both sexes and the incidence of oestrous cycle disorder increased at 500 mg/kg bw/d.

The clinical chemistry changes and adaptive liver changes at 500 mg/kg bw/d were not considered as adverse, while the high rate of oestrus cycle disorder at 500 mg/kg bw/d was. This finding gave rise to the need to investigate possible reproductive toxicity and endocrine disrupting effects of propoxylated BPA.

7.9.4.2. Human information

No relevant information available

7.9.4.3. Summary and discussion of repeated dose toxicity

A concern for systemic toxicity was identified in the OECD 422 study conducted with Grade 5 of BPA PO. However Grade 5 of BPA PO was ruled out as a test substance, therefore, Grade 4 of BPA PO was deemed as the most relevant test substance for this study.
The objective was to evaluate the potential toxicity of the test item following daily oral administration (gavage) to rats for 13 weeks. On completion of the treatment period, designated animals were held for a 4-week treatment-free period in order to evaluate the reversibility of any findings.
At 500 mg/kg bw/d, the test item induced adverse effects in males on the clinical condition, body weight and food consumption, leading to premature sacrifice of some of the animals, for ethical reasons. In high dose males, significantly lower body weight gain and body

weights, were noted from the beginning until the end of the treatment period. In large contrast to this, statistically significantly 18% higher mean body weight change were observed in females receiving 500 mg/kg/d.
The high dose caused slight to moderate changes in clinical pathology in both sexes, but most markedly in males. There were markedly higher liver weights in males and females that correlated with and microscopic hepatocellular hypertrophy, higher adrenal gland weights that correlated with the microscopic vacuolation of the adrenal cortex, higher kidney weights in females and decreased thymus weights in males correlated with the lymphoid atrophy. Cholesterol increases in high dose animals were +280% and + 195% in males and females, respectively.
At 120 mg/kg bw/d, the test item induced lower body weight and food consumption in males and slight changes in blood biochemistry parameters in both sexes. There were non-adverse findings in the liver, adrenals, kidneys, jejunum, GALT, prostate and seminal vesicles and sternum.
At 30 mg/kg bw/d, the test item induced lower body weight in males and slight, though statistically significant increases in cholesterol level in both sexes (17-22%). There were non-adverse findings in the liver, prostate and seminal vesicles.

Under the experimental conditions of the study, the No Observed Adverse Effect Level (NOAEL) after the 90-day treatment period was in the study report (Unpublished study report, 2018a) established at 120 mg/kg bw/d in males and at 500 mg/kg bw/d in females. This due to the adverse effect observed at 500 mg/kg bw/d in males.

The eMSCA finds that the marked cholesterol increases deserve some discussion, and that ignoring the cholesterol effects in the lower dose groups when setting the NOAEL may be incorrect. Especially since significant dose-dependent increases in cholesterol, levels were also observed in male and female rats in the TG 443 study with BPA 4PO. Further increasing the relevance of these findings is the fact that dose-dependent increases in cholesterol levels were also observed in TG 422 studies with BPA 2PO and BPA 5PO, indicating that this cholesterol increase could be a common effect caused by several different grades of propoxylated BPA - test compounds which otherwise seem to differ somewhat in their toxicity and potency.

The eMSCA also finds that the increased body weight gain seen in the high dose females from the 90-day study with BPA 4PO were likely test item related and deserve some more discussion. In the study report, these statistically significant changes were considered not to be test-item related, and the argumentation used was that the effect was seen during the whole study, including the treatment-free period. The eMSCA however finds that the fact that the females did not lose weight during the treatment free period, and therefore did not reach the body weight of control females, cannot be used as an argument against a treatment-related body weight increase during the treatment period. Furthermore, the effect pattern was very similar to the one observed in the EOGRTS, where females exposed to the highest tested dose of 540/360 mg/kg bw/day also gained significantly more weight than control females, whereas females exposed to a dose of 180 mg/kg bw/day did not. Opposite to the cholesterol effects, which were observed after exposure to several grades of propoxylated BPA, no indications of increased female body weights were seen in the TG 422 studies with both BPA 2PO and BPA 5PO.

7.9.5. Mutagenicity

7.9.5.1. Non-human information

7.9.5.1.1. In vitro data

The results of in vitro genotoxicity studies are summarised in table 27.

Table 27.

IN VITRO GENOTOXICITY STUDIES		
Method	**Results**	**Remarks**
bacterial reverse mutation assay (e.g. Ames test) (gene mutation) *S. typhimurium* TA 1535, TA 1537, TA 98 and TA 100 (met. act.: with and without) E. coli WP2 uvr A (met. act.: with and without) Test concentrations: -S9 mix: 0, 156, 313, 625, 1250, 2500, 5000µg/plate (TA100, TA1535, TA98, TA1537 and WP2 uvrA) +S9 mix: 0, 156, 313, 625, 1250, 2500, 5000µg/plate (TA100, TA1535, TA98, TA1537 and WP2 uvrA) Positive control substance(s): 9-aminoacridine Positive control substance(s): sodium azide Positive control substance(s): 2-acetylaminofluorene Positive control substance(s): 2-AA OECD Guideline 471 (Bacterial Reverse Mutation Assay)	Evaluation of results: negative Test results: negative for S. typhimurium TA 1535, TA 1537, TA 98 and TA 100(all strains/cell types tested) ; met. act.: with and without ; cytotoxicity: no, but tested up to limit concentrations ; vehicle controls valid: yes; negative controls valid: not applicable; positive controls valid: yes negative for E. coli WP2 uvr A(all strains/cell types tested) ; met. act.: with and without ; cytotoxicity: no, but tested up to limit concentrations ; vehicle controls valid: yes; negative controls valid: not applicable; positive controls valid: yes	Klimisch 2 (reliable with restrictions) supporting study read-across from supporting substance (structural analogue or surrogate) **Test material** Inconsistent substance ID information reported in the registration dossier. Form: viscous

mammalian cell gene mutation assay (gene mutation) mouse lymphoma L5178Y cells (met. act.: with and without) Positive control substance(s): methylmethanesulfonate (In the absence of S9 mix.) Positive control substance(s): benzo(a)pyrene (in the presence of S9 mix.) OECD Guideline 476 (In vitro Mammalian Cell Gene Mutation Test)	Test results: negative for mouse lymphoma L5178Y cells(all strains/cell types tested) ; met. act.: with and without ; vehicle controls valid: yes; negative controls valid: not applicable; positive controls valid: yes	Klimisch 1 (reliable without restriction) weight of evidence experimental result **Test material** **BPA 5PO (UVCB)** Form: viscous
mammalian cell gene mutation assay (gene mutation) Chinese hamster lung fibroblasts (V79) (met. act.: with and without) Test concentrations: first assay: -S9: 0, 10, 25, 50, 75, 100, 150 µg/mL; +S9: 0, 10, 20, 40, 80, 100 µg/mL second assay: -S9: 0, 25, 50, 75, 100, 125 µg/mL; +S9: 0, 25, 50, 75, 100, 125, 150 µg/mL supplementary assay: -S9: 0, 130, 140, 150 µg/mL; +S9: 0, 160, 180, 200 µg/mL Positive control substance(s): ethylmethanesulphonate (7,12-dimethylbenzanthracene (DMBA)) OECD Guideline 476 (In vitro Mammalian Cell Gene Mutation Test)	Evaluation of results: negative Test results: negative for Chinese hamster lung fibroblasts (V79) ; met. act.: with and without ; cytotoxicity: yes (from 130 µg/mL onwards -S9, from 160 µg/mL onwards +S9) ; vehicle controls valid: yes; positive controls valid: yes	Klimisch 2 (reliable with restrictions) weight of evidence read-across from supporting substance (structural analogue or surrogate) **Test material** **BPA 2PO** Form: solid

bacterial reverse mutation assay (e.g. Ames test) (gene mutation) *S. typhimurium* TA 1535, TA 1537, TA 98 and TA 100 (met. act.: with and without) E. coli WP2 uvr A (met. act.: with and without) Test concentrations: 5 to 5000 ug per plate Positive control substance(s): N-ethyl-N-nitro-N-nitrosoguanidine Positive control substance(s): 9-aminoacridine Positive control substance(s): 4-nitroquinoline-N-oxide Positive control substance(s): aminoanthracene OECD Guideline 471 (Bacterial Reverse Mutation Assay)	Evaluation of results: negative with metabolic activation negative without metabolic activation Test results: negative(all strains/cell types tested) ; met. act.: with and without ; vehicle controls valid: yes; negative controls valid: not applicable; positive controls valid: yes	Klimisch 2 (reliable with restrictions) weight of evidence read-across from supporting substance (structural analogue or surrogate) **Test material** Inconsistent substance ID information reported in the registration dossier Form: viscous
bacterial reverse mutation assay (e.g. Ames test) (gene mutation) *S. typhimurium* TA 1535, TA 1537, TA 98 and TA 100 (met. act.: with and without) Test concentrations: 25-79-250-790-2500 µg/plate Positive control substance(s): benzo(a)pyrene (2-nitrofluorene, sodium azide, 2-aminoanthracene, 9-aminoacridine,)	Evaluation of results: negative Test results: negative for S. typhimurium TA 1535, TA 1537, TA 98 and TA 100(all strains/cell types tested) ; met. act.: with and without ; cytotoxicity: yes (at 2500 µg/plate) ; vehicle controls valid: yes; negative controls valid: yes; positive controls valid: yes	Klimisch 2 (reliable with restrictions) weight of evidence read-across from supporting substance (structural analogue or surrogate) **Test material** **BPA 2PO** Form: solid

OECD Guideline 471 (Bacterial Reverse Mutation Assay)		
in vitro mammalian chromosome aberration test (chromosome aberration) Chinese hamster lung fibroblasts (V79) (met. act.: with and without) Test concentrations: -S9 mix (short- term treatment): 0, 12.5, 25, 50, 75, 100µg/mL +S9 mix (short term treatment): 0, 25, 50, 100, 150, 200µg/mL -S9 mix (continuous treatment, 24 and 48 hrs): 0, 6.25, 12.5, 25, 50, 100µg/mL The maximum concentration was established based on the growth inhibition test. In this test, more than 50% growth inhibition was observed at 93.75-750µg/mL for short-term treatment without S9, 187.5-750µg/mL with S9, and >93.75µg/mL for 24 hrs and 46.88µg/mL for 48 hrs continuous treatment. More than 1500µg/mL , the growth seemed to recover by deposition of test material, Positive control substance(s): N-ethyl-N-nitro-N-nitrosoguanidine Positive control substance(s): benzo(a)pyrene Positive control substance(s): N-ethyl-N-nitro-N-nitrosoguanidine	Evaluation of results: negative Test results: negative for Chinese hamster lung fibroblasts (V79) ; met. act.: with and without ; cytotoxicity: In short-term treatment cytotoxicity was observed at 75 and 100µg/mL without S9, and 150 and 200µg/mL with S9. In continuous treatment, at 100µg/mL.	Klimisch 1 (reliable without restriction) weight of evidence experimental result **Test material** **BPA 5PO (UVCB)** Form: viscous

OECD Guideline 473 (In vitro Mammalian Chromosome Aberration Test)		

Evaluating MSCA comment

The information is reported as presented by the Registrant(s) and has not been reviewed by the eMSCA. However, it is noted that inconsistent information is given on the identity of the tested substance in two of the *in vitro* studies. This should be clarified/corrected by the Registrant(s).

7.9.5.2. Human information

No relevant information available.

7.9.5.3. Summary and discussion of mutagenicity

Not reviewed by the evaluating MSCA.

7.9.6. Carcinogenicity

7.9.6.1. Non-human information

No relevant information available.

7.9.6.2. Human information

No relevant information available.

7.9.7. Toxicity to reproduction (effects on fertility and developmental toxicity)

7.9.7.1. Effects on fertility

7.9.7.1.1. Non-human information

The results of studies on fertility are summarised in table 28.

Table 28.

STUDIES ON FERTILITY		
Method	**Results**	**Remarks**
rat (Sprague-Dawley) male/female extended one-generation reproductive toxicity - with both developmental neuro- and immunotoxicity (Cohorts 1A, 1B without extension, 2A, 2B, and 3) oral: gavage 0mg/kg bw/day (nominal) 60mg/kg bw/day (nominal) 180mg/kg bw/day (nominal) 360mg/kg bw/day (nominal) In the first instance, 540 mg/kg bw/day was selected as the high dose level. After 6 days of treatment, 3 males from the high dose-group had severe clinical signs and body weight losses. Therefore it was decided to: - lower the high-dose level to 360 mg/kg bw/day Vehicle: olive oil Exposure: P Generation - in the males (at least 10 weeks of treatment): 2 weeks before mating, during the mating period (up to 2 weeks), until euthanasia (after weaning of the pups), - in the females (at least 8 to 10 weeks of treatment): 2 weeks before mating, during the mating period (up to 2 weeks), during gestation, during lactation until Day 21 p.p. (or Day 22 p.p. sacrifice after haematology, blood chemistry and urinalysis on Day 23 p.c. for the selected females), until euthanasia for females with no evidence of mating or no delivery (26 days after the last day of the mating period). Cohort 1A - in the males and females: from weaning (Day 22 p.p.), until euthanasia (from Days	**First parental generation (P0)** NOAEL (PO) 180 mg/kg bw/day (male/female) based on: organ weights and organ / body weight ratios ; histopathology: non-neoplastic ; reproductive function (oestrous cycle); Thyroid hormones **F1 generation** NOAEL (PO): 180 mg/kg bw/day (male/female) based on: organ weights and organ / body weight ratios ; histopathology: non-neoplastic **F2 generation** NOAEL (PO): 360 mg/kg bw/day (male/female) based on: clinical signs ; mortality ; body weight and weight gain **Overall reproductive toxicity** Yes Lowest effective dose / concentration 180mg/kg bw/day. Relation to other toxic effects: reproductive effects occurring together with other toxic effects, but not as a secondary non-	Klimisch 1 (reliable without restriction) key study experimental study **Test material BPA 4PO** 4,4'-Isopropylidenediphenol, propoxylated / CAS 37353-75-6 / Sample 3 **Reference** Unpublished study report, 2018b

98 to 101 p.p.). Cohort 1B - in the males: from weaning (Day 22 p.p.) for at least 10 weeks before mating, during the mating period (up to 2 weeks), after sacrifice of F2 pups (on Day 4 p.p.), - in the females: from weaning (Day 22 p.p.) for at least 10 weeks before mating, during the mating period (up to 2 weeks), during gestation, during lactation until Day 4 p.p. inclusive, until euthanasia for females with no evidence of mating or no delivery (24-26 days after the last day of the mating period). Performed according to OECD Guideline 443 (Extended One-Generation Reproductive Toxicity Study)	specific consequence of other toxic effects	
rat (Crl:WI(Han)) male/female combined 28-day repeated dose and reproduction/developmental screening oral: gavage 0, 125, 250, 500 mg/kg/day (actual ingested) Vehicle: polyethylene glycol (specific gravity 1.125) Exposure: Males were exposed for 29 days, i.e. 2 weeks prior to mating, during mating, and up to the day prior to scheduled necropsy. Females were exposed for 43-54 days, i.e. during 2 weeks prior to mating, during mating, during post-coitum, and during at least 4 days of lactation (up to the day prior to scheduled necropsy). One females of Group 1 and one of Group 3 were not dosed during littering. Pups were not treated directly, but were potentially exposed to the test substance in utero and through lactational transfer. (Once daily for 7 days per week, approximately the same time each day with a maximum of 6 hours difference between the earliest and latest dose. Animals were dosed up to the	NOAEL (P): 125 mg/kg bw/day (actual dose received) (male/female) based on: Toxicologically relevant effects on mortality, clinical signs, body weight, food consumption, food efficiency, gross pathology, organ weights and histopathology were seen at 250 and 500 mg/kg. NOAEL (Reproduction) (P): 250 mg/kg bw/day (actual dose received) (male/female) based on: Effects on reproductive performance of parental animals and impaired spermatogenesis. NOAEL (Developmental) (F1): >= 500 mg/kg bw/day (actual dose received) (male/female) based on: Highest dose tested	Klimisch 2 (reliable with restrictions) supporting study **Test material** **BPA 2PO** Form: powder **Reference** Unpublished study report, 2011

day prior to the scheduled necropsy.) OECD Test Guideline 422 (Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test) EPA, Health Effects Test Guidelines OPPTS 870.3650, Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test, July 2000.		
rat (Crj: CD(SD)) male/female combined repeated dose and reproduction/developmental screening oral: gavage 0 mg/kg b.w./day 30 mg/kg b.w./day 120 mg/kg b.w./day 500 mg/kg b.w./day Vehicle: olive oil Exposure: Males: 42 days Females: 42-53 days, from 14 days before mating to day 4 of lactation (Once a day) OECD Guideline 422 (Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test)	NOEL (Repeated): 30 mg/kg bw/day (male/female) based on: Dilatation of lacteal in small intestine observed at 120 mg/kg/day. NOEL (P): 120 mg/kg bw/day (female) based on: Reproductive potential. The high rate of oestrous cycle disorder observed at 500 mg/kg/day. NOEL (F1): 120 mg/kg bw/day based on: Development of newborn. The decrease of body weight observed at 500 mg/kg/day.	Klimisch 2 (reliable with restrictions) supporting study experimental result **Test material** **BPA 5PO** Form: viscous **Reference** Ministry of Health, Labour and Welfare, Japan, 2010

As specified in the Decision, the TG422 screening study on reproductive toxicity for Grade 5 of BPA PO indicated possible reproductive toxicity effect of Grade 5 of BPA PO. However, the findings did not fulfil the criteria for reproductive toxicity classification according to the eMSCA. The results concerning indications of an increased rate of oestrus cycle disorder in females (Grade 5 of BPA PO) in the screening study caused a concern for endocrine disruption *in vivo*. Further evaluation by QSAR model predictions on oestrogen receptor performed by the eMSCA indicated a potential concern that BPA PO may cause reproduction toxicity and endocrine disrupting activity through binding of constituents of BPA PO to the oestrogen receptor. To clarify the indications of concern on reproductive toxicity, the eMSCA requested an Extended-One Generation Reproductive Toxicity Study (EOGRTS) in accordance with the OECD Testing Guideline 443. This Guideline includes parameters for adverse effects on reproduction and a number of endocrine sensitive parameters, which may be used to inform about endocrine disrupting modes of action.

Based on the results obtained during the screening for toxicity to reproduction, it was concluded that Grade 5 of BPA PO represented a greater concern than BPA 2PO, considering the high rate of oestrus cycle disorder induced by Grade 5 of BPA PO. However, Grade 5 of BPA PO can be regarded as a polymer under REACH, so it was ruled out as a test substance for the purpose of the EOGRTS. Since the outcome of the OECD 422 suggested that potential endocrine-disrupting properties could be related to higher degrees of propoxylation and therefore constituents with higher chain-length, Grade 4 of BPA PO was deemed as the most relevant test substance for this study by the eMSCA.

Extended-One Generation Toxicity to Reproduction Study

The EOGRTS (Unpublished study report, 2018b) was performed with all cohorts (including cohort 1B to generate the F2 generation, 2A/2B for investigation of developmental neurotoxicity and cohort 3 for investigation of immunotoxicity).

The test item, 4,4'-Isopropylidenediphenol, propoxylated, Grade 4PO, was administered daily by oral gavage, at dose levels of 60, 180 or 540/360 mg/kg bw/d, to sexually-mature male and female rats (parental (P) generation) starting 2 weeks before mating and continuously through mating, gestation and weaning of their pups (F1 generation). In the first instance, 540 mg/kg bw/day was selected as the high dose level. After 6 days of treatment, three males from the high dose-group had severe clinical signs and body weight losses. Therefore, it was decided to lower the high-dose level to 360 mg/kg bw/day.

At weaning, the F1 generation was also exposed to graduated doses of the test item while being assigned to Cohorts of animals for reproductive/developmental toxicity, developmental neurotoxicity or developmental immunotoxicity testing.

Fertility results from this EOGRT study are reported and discussed in section 7.9.7.3.

Screening for toxicity to reproduction conducted on BPA 2PO

The test substance was administered by daily oral gavage to male and female Wistar Han rats at dose levels of 125, 250 and 500 mg/kg bw/day. Males were exposed for 2 weeks prior to mating, during mating, and up to termination (for 29 days). The females were exposed for 2 weeks prior to mating, during mating, during post-coitum, and at least 4 days of lactation (for 43-54 days). Formulation analysis showed that the formulations were prepared accurately, were homogenous, and were stable for at least 6 hours at room temperature.

Some sperm parameters were adversely affected in the TG422 study with BPA 2PO. Impaired spermatogenesis was noted for males exposed to 250 and 500 mg/kg, with changes in sperm release seen in 2/7 (250 mg/kg) and 5/10 (500 mg/kg) males and spermatid retention in tubule stage X/XI observed in 2/5 (250 mg/kg) males. The mating, fertility and conception indices were lower for females at 500 mg/kg bw/d, along with a lower number of corpora lutea. The high mortality and limited number of litters available for evaluation likely contributed to this, though when also taking into account the evidence of impaired spermatogenesis, a treatment related effect cannot be excluded. There were no toxicologically significant changes noted in any of the remaining reproductive parameters investigated in this study (i.e. gestation index, precoital time, and number of implantation sites).

No developmental toxicity was observed up to 500 mg/kg bw/d. Due to mortality there was a lower number of litters available for assessment at 500 mg/kg bw/d, and a higher incidence of pup mortality, a lower number of living pups, and a higher number of dead pups was seen at this dose level. However, all pup mortality was attributable to a single dam and was secondary to maternal toxicity.

No treatment-related changes were noted in any of the remaining developmental parameters investigated in this study (i.e. duration of gestation, parturition, maternal care and clinical signs, body weights and macroscopy of pups).

In conclusion, treatment with BPA 2PO by oral gavage in male and female Wistar Han rats at dose levels of 125, 250 and 500 mg/kg bw/day revealed parental toxicity at 250 and 500 mg/kg bw/day, and reproduction toxicity at 500 mg/kg bw/day.

Screening for toxicity to reproduction conducted on Grade 5 of BPA PO
The test substance was administered by daily oral gavage to male and female Sprague-Dawley rats at dose levels of 30, 120 and 500 mg/kg bw/day. Males were exposed for 42 days. The females were exposed for 2 weeks prior to mating, during mating, during post-coitum, and at least 4 days of lactation (for 42-53 days).
Incidence of oestrous cycle disorder increased at 500 mg/kg bw/d (5/17 compared to 0/17 in controls). No abnormal findings in pairing days until copulation, copulation index, gestation index, gestation length, number of corpora lutea, number of implantation sites, implantation index, fertility index, delivery index and delivery/lactation behaviour.
Decrease in body weight of pups was observed at 500 mg/kg bw/d. There were no changes in number of pups born, number of pups alive, sex ratio, live birth index, external findings and viability index caused by treatment with test substance.
In conclusion, treatment with Grade 5 of BPA PO resulted in high rate of oestrus cycle disorder and decrease in body weight of pups observed at 500 mg/kg bw/d.

7.9.7.2. Developmental toxicity

Table 29.

STUDIES ON DEVELOPMENT		
Method	**Results**	**Remarks**
rat (Sprague-Dawley [rat]) oral: gavage 0mg/kg bw/day (actual dose received) 180mg/kg bw/day (actual dose received) 360mg/kg bw/day (actual dose received) 720mg/kg bw/day (actual dose received) Vehicle: olive oil Exposure: The dose formulations were administered daily from Day 6 to Day 20 p.c., inclusive. OECD Guideline 414 (Prenatal Developmental Toxicity Study)	**Maternal animals:** NOAEL: 180 mg/kg bw/day (actual dose received) based on: Mortality, body weight and weight gain, food consumption. **Fetuses:** NOAEL: 360 mg/kg bw/day based on: external malformations, skeletal malformations, visceral malformations, embryo-fetal toxicity **Overall developmental toxicity:** yes Lowest effective dose / concentration: 720mg/kg bw/day (nominal) Relation to maternal toxicity: developmental effects as a secondary non-specific consequence of maternal toxicity effects	Klimisch 1 (reliable without restriction) key study experimental study **Test material** **BPA 4PO** 4,4'-Isopropylidenediphenol, propoxylated / CAS 37353-75-6 / Sample 3 Form: liquid **Reference** Unpublished study report, 2018c
rat (Sprague-Dawley) male/female extended one-generation	**First parental generation (P0)**	Klimisch 1 (reliable without restriction)

reproductive toxicity - with both developmental neuro- and immunotoxicity (Cohorts 1A, 1B without extension, 2A, 2B, and 3) oral: gavage 0mg/kg bw/day (nominal) 60mg/kg bw/day (nominal) 180mg/kg bw/day (nominal) 360mg/kg bw/day (nominal) In the first instance, 540 mg/kg bw/day was selected as the high dose level. After 6 days of treatment, 3 males from the high dose-group had severe clinical signs and body weight losses. Therefore it was decided to: - lower the high-dose level to 360 mg/kg bw/day Vehicle: olive oil Exposure: P Generation - in the males (at least 10 weeks of treatment): 2 weeks before mating, during the mating period (up to 2 weeks), until euthanasia (after weaning of the pups), - in the females (at least 8 to 10 weeks of treatment): 2 weeks before mating, during the mating period (up to 2 weeks), during gestation, during lactation until Day 21 p.p. (or Day 22 p.p. sacrifice after hematology, blood chemistry and urinalysis on Day 23 p.c. for the selected females), until euthanasia for females with no evidence of mating or no delivery (26 days after the last day of the mating period). Cohort 1A - in the males and females: from weaning (Day 22 p.p.), until euthanasia (from Days 98 to 101 p.p.). Cohort 1B - in the males: from weaning (Day 22 p.p.) for at least 10 weeks before mating, during the mating period (up to 2 weeks), after sacrifice of F2 pups (on Day 4 p.p.), - in the females: from weaning (Day 22 p.p.) for at least 10 weeks before mating, during the mating period (up to 2 weeks), during gestation, during lactation until Day 4 p.p. inclusive, until euthanasia for females with no evidence of mating or no delivery (24-26 days after the last day of the mating period). Cohort 2A - in	NOAEL (PO) 180 mg/kg bw/day (male/female) based on: organ weights and organ / body weight ratios ; histopathology: non-neoplastic ; reproductive function (estrous cycle); Thyroid hormones **F1 generation** NOAEL (PO): 180 mg/kg bw/day (male/female) based on: organ weights and organ / body weight ratios ; histopathology: non-neoplastic **F2 generation** NOAEL (PO): 360 mg/kg bw/day (male/female) based on: clinical signs ; mortality ; body weight and weight gain **Overall reproductive toxicity** Yes Lowest effective dose / concentration 180mg/kg bw/day. Relation to other toxic effects: reproductive effects occurring together with other toxic effects, but not as a secondary non-specific consequence of other toxic effects	key study experimental study **Test material** **BPA 4PO** 4,4'-Isopropylidenediphenol, propoxylated / CAS 37353-75-6 / Sample 3 **Reference** Unpublished study report, 2018b

the males and females: from weaning (Day 22 p.p.), until euthanasia (after completion of behavioural testing: Days 75 to 78 p.p.). Cohort 2B There was no direct dosing in Cohort 2B animals (sacrificed on Day 22 p.p.). Cohort 3 - in the males and females: from weaning (Day 22 p.p.), until 5 days after KLH injection on Day 56 (± 3) p.p. (sacrifice on Day 61 (± 3) p.p.). (Daily) OECD Guideline 443 (Extended One-Generation Reproductive Toxicity Study)		
rat (Crl:WI(Han)) male/female combined 28-day repeated dose and reproduction/developmental screening oral: gavage 0, 125, 250, 500 mg/kg/day (actual ingested) Vehicle: polyethylene glycol (specific gravity 1.125) Exposure: Males were exposed for 29 days, i.e. 2 weeks prior to mating, during mating, and up to the day prior to scheduled necropsy. Females were exposed for 43-54 days, i.e. during 2 weeks prior to mating, during mating, during post-coitum, and during at least 4 days of lactation (up to the day prior to scheduled necropsy). One females of Group 1 and one of Group 3 were not dosed during littering. Pups were not treated directly, but were potentially exposed to the test substance in utero and through lactational transfer. (Once daily for 7 days per week, approximately the same time each day with a maximum of 6 hours difference between the earliest and latest dose. Animals were dosed up to the day prior to the scheduled necropsy.)	NOAEL (P): 125 mg/kg bw/day (actual dose received) (male/female) based on: Toxicologically relevant effects on mortality, clinical signs, body weight, food consumption, food efficiency, gross pathology, organ weights and histopathology were seen at 250 and 500 mg/kg. NOAEL (Reproduction) (P): 250 mg/kg bw/day (actual dose received) (male/female) based on: Effects on reproductive performance of parental animals and impaired spermatogenesis.) NOAEL (Developmental) (F1): >= 500 mg/kg bw/day (actual dose received) (male/female) based on: test mat.	Klimisch 2 (reliable with restrictions) supporting study **Test material BPA 2PO** Form: powder **Reference** Unpublished study report, 2011

OECD Guideline 422 (Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test)		
rat (Crj: CD(SD)) male/female combined repeated dose and reproduction/development screening oral: gavage 0 mg/kg b.w./day 30 mg/kg b.w./day 120 mg/kg b.w./day 500 mg/kg b.w./day Vehicle: olive oil Exposure: Males: 42 days Females: 42-53 days, from 14 days before mating to day 4 of lactation (Once a day) OECD Guideline 422 (Combined Repeated Dose Toxicity Study with the Reproduction / Developmental Toxicity Screening Test)	NOEL (Repeated): 30 mg/kg bw/day (male/female) based on: Dilatation of lacteal in small intestine observed at 120 mg/kg/day. NOEL (P): 120 mg/kg bw/day (female) based on: Reproductive potential. The high rate of oestrous cycle disorder observed at 500 mg/kg/day. NOEL (F1): 120 mg/kg bw/day based on: Development of newborn. The decrease of body weight observed at 500 mg/kg/day.	Klimisch 2 (reliable with restriction) supporting study experimental result **Test material** **BPA 5PO** Form: viscous **Reference** Ministry of Health, Labour and Welfare, Japan, 2010

Based on the results obtained during the screening for toxicity to reproduction, it was concluded that Grade 5 of BPA PO represented a greater concern than BPA 2PO, considering developmental findings with a decrease of pup body weights observed at 500 mg/kg bw/d with Grade 5 of BPA PO. The potential endocrine modulating effect of BPA PO also strengthened the concern for developmental effects that needed to be investigated in the prenatal developmental toxicity study, thus justifying the study to be conducted on a substance with a high degree of propoxylation and containing constituents with high chain-length as previously discussed. However, Grade 5 of BPA PO can be regarded as a polymer under REACH, so it was a ruled out as a test substance for the purpose of the developmental toxicity/teratogenicity testing. Therefore, Grade 4 of BPA PO was deemed as the most relevant test substance for this study by the eMSCA.

Developmental toxicity / Teratogenicity study (OECD TG 414) on BPA 4PO

Developmental toxicity/teratogenicity of the registered substance (Unpublished study report, 2018c) was investigated during a GLP-compliant study, conducted in accordance with the OECD Testing Guideline 414 on Grade 4 of BPA PO.

Three groups of 24 time-mated female Sprague-Dawley rats received the test item, at 180, 360 or 720 mg/kg bw/d by oral route (gavage) once daily from Days 6 to 20 p.c. A constant dosage-volume of 5 mL/kg/day was used. Another group of 24 rats received the vehicle alone (olive oil) under the same experimental conditions, and acted as a control group. Formulation concentrations were checked in the start and end of the treatment period. The animals were checked daily for mortality and clinical signs. Body weight and food consumption were recorded every 2 to 3 days. On Day 21 p.c., females were sacrificed and submitted to a macroscopic post-mortem examination. Hysterectomy was performed and

the numbers of corpora lutea, uterine scars, implantations, early and late resorptions, and live and dead foetuses were recorded. The live foetuses were sexed, weighed and examined for external, soft tissues and skeletal (cartilages + bones) abnormalities.
In parent animals from the 720 mg/kg bw/d group, there were eight unscheduled deaths. Taking into account the similarity of the findings associated to these deaths (clinical signs, effects on body weight/food consumption and macroscopic examination at necropsy), this mortality was considered to be related to the test item treatment. In surviving animals from the highest dose group, most of clinical signs (soiled urogenital area, lateral decubitus, piloerection, emaciated appearance, round back, cold to the touch, hypoactivity, abdominal breathing and/or eyes half-closed) were similar to those recorded in prematurely sacrificed and/or found dead animals. They were considered treatment-related and adverse. Statistically significant changes in body weight, body weight gain and food consumption were observed from 360 mg/kg bw/d, which were considered as treatment-related and adverse.
In the highest-dose there was a lower percentage of live foetuses per animal as a consequence of increased resorptions (late, early and scars) and dead foetuses which resulted in an increased incidence of mean percent of post-implantation loss. Foetuses (males and females) had a lower mean body weight, and malformations such as local oedema, cleft lip, anasarca, visceral oedema, fluid-filled thoracic cavity, fluid-filled abdomen, foetal variations (unossified bones or bones with incomplete ossification), and split supraoccipital. All these findings were considered treatment-related and adverse in a context of excessive maternal toxicity. On the basis of the results obtained in this study the NOAEL for maternal parameters was considered 180 mg/kg bw/d, based on adverse effects on body weight, body weight change and food consumption from 360 mg/kg bw/d and mortality at 720 mg/kg bw/d. The No Observed Adverse Effect Level (NOAEL) for embryo-foetal development was considered 360 mg/kg bw/d, based on embryo/foetal toxicity associated with malformations in a context of excessive maternal toxicity at 720 mg/kg bw/d.

Extended-One Generation Toxicity to Reproduction Study on BPA 4PO
The EOGRTS (Unpublished study report, 2018b) was performed with all cohorts (including cohort 1B to generate the F2 generation, 2A/2B for investigation of developmental neurotoxicity and cohort 3 for investigation of immunotoxicity).
The test item, 4,4'-Isopropylidenediphenol, propoxylated, Grade 4PO, was administered daily by oral gavage, at dose levels of 60, 180 or 540/360 mg/kg bw/d, to sexually-mature male and female rats (parental (P) generation) starting 2 weeks before mating and continuously through mating, gestation and weaning of their pups (F1 generation). At weaning, F1 generation was also exposed to graduated doses of the test item while being assigned to Cohorts of animals for reproductive/developmental toxicity, developmental neurotoxicity or developmental immunotoxicity testing.
Developmental toxicity results from this EOGRT study are reported and discussed in section 7.9.7.3.

Screening for toxicity to reproduction conducted on BPA 2PO
The test substance was administered by daily oral gavage to male and female Wistar Han rats at dose levels of 125, 250 and 500 mg/kg bw/day. Males were exposed for 2 weeks prior to mating, during mating, and up to termination (for 29 days). The females were exposed for 2 weeks prior to mating, during mating, during post-coitum, and at least 4 days of lactation (for 43-54 days). Formulation analysis showed that the formulations were prepared accurately, were homogenous, and were stable for at least 6 hours at room temperature.
No developmental toxicity was observed up to 500 mg/kg bw/d. Due to mortality there was a lower number of litters available for assessment at 500 mg/kg bw/d, and a higher incidence of pup mortality, a lower number of living pups, and a higher number of dead pups was seen at this dose level. However, all pup mortality was attributable to a single dam and was secondary to maternal toxicity. No treatment-related changes were noted in any of the remaining developmental parameters investigated in this study (i.e. duration of gestation, parturition, maternal care and clinical signs, body weights and macroscopy of

pups). In conclusion, treatment with BPA 2PO by oral gavage in male and female Wistar Han rats at dose levels of 125, 250 and 500 mg/kg bw/day revealed parental toxicity at 250 and 500 mg/kg bw/day, and reproduction toxicity at 500 mg/kg bw/day.

Screening for toxicity to reproduction conducted on Grade 5 of BPA PO
The test substance was administered by daily oral gavage to male and female Sprague-Dawley rats at dose levels of 30, 120 and 500 mg/kg bw/day. Males were exposed for 42 days. The females were exposed for 2 weeks prior to mating, during mating, during post-coitum, and at least 4 days of lactation (for 42-53 days).
Decrease in body weight of pups was observed at 500 mg/kg bw/d. There were no changes in number of pups born, number of pups alive, sex ratio, live birth index, external findings and viability index caused by treatment with test substance. In conclusion, treatment with Grade 5 of BPA PO resulted in high rate of oestrus cycle disorder and decrease in body weight of pups observed at 500 mg/kg bw/d.

7.9.7.3. Summary and discussion of reproductive toxicity

Fertility males

Some signs of adverse effects on male fertility were observed in the performed repeated dose toxicity and reproductive toxicity screening studies with BPA 2PO, 4PO and 5PO, though mostly in the high dose groups, where much systemic toxicity was also observed. In contrast, no adverse effects were seen on reproductive organ weights or histo-pathology in parental males from the TG 443 study with BPA 4PO, whereas a few significant effects were noted in the offspring. Whether these were developmental effects or effects on fertility caused by exposure in adulthood is difficult to discern. Below, the most relevant findings on the male reproductive system are summarised.
Some **sperm parameters** were affected in the TG 422 study with BPA 2PO. Impaired spermatogenesis was noted for males exposed to 250 and 500 mg/kg, with changes in sperm release seen in 2/7 (250 mg/kg) and 5/10 (500 mg/kg) males and spermatid retention in tubule stage X/XI observed in 2/5 (250 mg/kg) males. In the TG 422 study with BPA 5PO, an effect on sperm parameters was also seen as the count in stage XII was significantly different from controls in the 500 mg/kg group. No other stages were significantly affected, which in itself could indicate a chance finding. However, seen together with significantly affected sperm parameters in the TG422 study with BPA 2PO, it could also indicate a real effect. In the TG 443 study, sperm quality was analysed in P-generation and F1 males, and no adverse effects were observed in any exposure group. It is hence plausible that the different grades of BPA PO affect sperm parameters differently.
In the TG 408 study with BPA 4PO, small **seminal vesicles** were seen in 1/7 high dose males, a finding which was correlatated with acinar atrophy. In addition, dose-related decreases in secretory content from the seminal vesicles was seen (2/10 males in 30 mg/kg/day, 1/10 males in 120 mg/kg/day and 4/7 males in 500 mg/kg/day). Seminal vesicles also showed reduced contents in 4/5 high does males (500 mg/kg) in the TG 422 study with BPA-2PO. In contrast, no exposure related effects in seminal vesicles were observed in either parental males or offspring the TG 443 study with BPA 4PO.

In the TG 408 study, 5/7 high dose males showed minimal to slight acinar atrophy in the **prostate,** and decreased secretory content was present in all three dose groups (2/10 in 30 mg/kg/day, 3/10 in 120 mg/kg/day and 5/7 in 500 mg/kg/day). Reduced prostate gland content was also noted in 1/5 high dose (500 mg/kg) males in the TG 422 study with BPA 2PO.
In the parental generation from the TG 443 study, no adverse effects on the prostate were observed. In the offspring however, statistically significant reduced prostate weights were recorded in males treated at 360 mg/kg/day in cohort 1B. The absolute prostate weights were 17% decreased compared to controls, and a non-significant 11.2% decrease in relative prostate weight was seen. Additionally, all other mean prostate

weights in the high dose groups males from the other cohorts were also reduced (though not significantly). In cohort 2A, the effects were most pronounced, with a 12.9% (absolute) & 14.0% (relative) decrease. In cohort 3, the decrease was 9.2% (absolute) and 8.05% (relative) and in Cohort 1A, the decrease was 11.4% (absolute) & 7.6% (relative). The smallest effect was seen in cohort 2B, where the decrease in prostate weight was only 5.8% (absolute) and 2.6% (relative). In the study report, the significant effect on prostate weight in cohort 1B was described as probably not related to the test item administration. However, using an overall weight of evidence approach, the eMSCA considers as unlikely that all prostate weights (both absolute and relative) in high dose animals should be smaller than in control animals, and histopathologically affected in the TG 408 study if this was not a substance related effect.

Fertility females

In the TG 422 study with grade BPA 5PO, an increased rate of **oestrous cycle disorder** was observed at 500 mg/kg/day. Oestrous cyclicity disruptions were also observed in the high dose females (540/360 mg/kg/day) from the parental generation in the EOGRTS with BPA 4PO. A statistically significant increase in mean number of days of diestrus was seen (7.3 *vs.* 5.0 days in controls), resulting in a prolonged duration of mean oestrous cycle (5.4 days *vs.* 3.9 days) and a decreased mean number of cycles (3.0 vs. 2.0). This finding was considered test item related and adverse. In contrast to these findings, oestrous cycle irregularities were not observed in cohort 1A offspring. A possible explanation for the apparent discrepancy between findings in parental females and offspring could be that a higher dose than 360 mg/kg/day may be needed to elicit an effect on oestrous cyclicity. In the P-generation dams, oestrous cyclicity was measured shortly after the dose had been reduced from 540 mg/kg/day to 360 mg/kg/day. Hence, the high dose may have markedly affected the female endocrine/reproductive system, causing significant effects on oestrous cyclicity, which were not elicited by a dose of 360 mg/kg/day.
Hypertrophy/hyperplasia of the interstitial gland in the **ovaries** was noted at higher severity in 2/5 (250 mg/kg) and 3/5 (500 mg/kg) females in the TG 422 study with BPA 2PO. In the parental generation of the TG 443 study with BPA 4PO, adult exposure to BPA PO did not affect the number of ovarian primordial follicles on PCNA-stained slides (mean number was 11.4$\pm$6.0 in controls and 14.5$\pm$7.4 in high dose females). In the TG 408 study, also no adverse effects on weight of **ovary and uterus**, were noted and no histopathological findings were observed in the BPA PO exposed females at the end of the treatment period. However, at the end of treatment-free period there were markedly higher absolute and relative **uterus weights** in females previously treated at 500 mg/kg/day when compared to controls (+136% in absolute and +115% in relative). These differences were considered to be possibly related to the test item administration although not seen at the end of the treatment period and correlated with increased numbers of females in proestrus or oestrus than in controls.

Mating, fertility and delivery seemed to be marginally affected in the parental generation of the EOGRTS. In the high dose females (540/360 mg/kg/day), both a lower mating index and a lower fertility index was seen, effects which could be correlated to the observed cycle irregularities. In Cohort 1B, no mating, fertility or delivery parameters were significantly affected. In the TG 422 study with BPA-2PO, also significant decreases in mating index, fertility index and conception indexes were seen in the high dose group (500 mg/kg), along with a lower number of corpora lutea. It is stated in the study report that the high mortality and limited number of litters available for evaluation likely contributed to this, though when also taking into account evidence of impaired spermatogenesis, a treatment related effect cannot be excluded.

Developmental effects

In the TG 414 study, developmental toxicity effects were only observed at a dose that also caused severe maternal toxicity.
In the TG 443 study, there was no effects on **lactation index** (Days 4-21 *p.p.*) in F1 lactating pups, and no clinical signs in F1 lactating pups. There were also no test item treatment-related effects on mean **F1 body weight** or on body weight gain up to PND 21. The same picture was seen in the F2 generation, as no clinical signs were seen in F2 lactating pups, and no adverse effects on mean offspring body weight or body weight gain was observed, until PD 4 when they were terminated.
No statistically significant effects were observed on measurements of **anogenital distance** (AGD)**,** and no tendencies towards any effects were observed. Unfortunately, the variation in the AGD, both within litters and within each group, was very marked. This large variation could be due to imprecise method of AGD measurement or possibly large differences in how the animals are being held (stretched) when their AGD was being measured. In addition, the fact that the AGD was measured on PND4 instead of PND1 could increase the variability. Regardless of the reason, the resulting large variation would make it almost impossible to show subtle effects of chemicals, i.e. chemicals that only reduce AGD to a moderate degree. For instance, a reduction of 5-7% in AGD would probably not have been statistically significant, with a variation in the control group as seen in the present study. These methodological challenges with AGD measurement weaken the utility of the obtained AGD results, in relation to interpretation of whether BPA-PO, could cause subtle endocrine disrupting effects. However, based on the presented results, there were no indications that exposure to BPO PO affected male or female AGD.

Analysis of **nipple retention** also did not show any treatment related effects. When an examination of single animal data for nipple retention data was performed, another important shortcoming of the study was seen, in relation to the methodology used to obtain these early biomarkers for endocrine disrupting effects. For all (~400) examined male pups, zero retained nipples were recorded. Based on previous experience from a large number of scientific publications this is clearly incorrect as there is always a background incidence. When the accuracy with which the animals are being examined is this poor, unfortunately the results end up being very uninformative in relation to potential subtle anti-androgenic effects.

When compared with controls, there were no statistically significant differences in the mean age of **balanopreputial separation** in males, **vaginal opening** in females or mean time to first oestrous after vaginal opening in females in Cohort 1A, 1B, 2A or 3. Some apparent differences between group means were seen, but when examining the single animal data, it was clear that these were caused by the presence of 1-2 outliers, i.e. single animals that for some reason reached sexual maturation several weeks later than all the other animals in the group. The lack of overall treatment related effect on sexual development was further corroborated by the fact that no overlap in potential effects was seen between the different cohorts (1A, 1B, 2A, 3), for either male or female offspring.

Reproductive development in female offspring may have been affected by BPA PO exposure, when looking at the **number of primordial follicles** on PCNA-stained slides. In females from Cohort 1A, significant differences were observed between the control group and each of test item-treated groups 2, 3 and 4, regarding the total number of primordial follicles. At 60, 180 and 360 mg/kg/day the mean number was 7.53$\pm$2.02, 8.42$\pm$2.28, 9.63$\pm$5.29, respectively, whereas there were 15.57$\pm$6.3 primordial follicles in controls (mean number per section on PCNA-stained slides). In the study report, it is highlighted that the numbers should be compared to the total number of primordial follicles in control dams from the parental Cohort (11.42). Furthermore it is stated that the slight decrease in test item-treated females *versus* controls was of low magnitude, was not dose-related and with a high inter-individual variability. In addition, since there

was no in life reproduction abnormalities in Cohort 1A, a relationship to test item administration was considered unlikely. The eMSCA does not agree with this conclusion. In the parental generation, adult exposure to BPA-PO females did not significantly affect the number of primordial follicles (mean number was 11.4±6.0 in controls and 14.5±7.4 in high dose females). Hence, a control value with a mean of 15.6 seems to be within the normal range. A treatment related effect cannot be excluded based on the presented results, and the fact that no reproductive abnormalities were seen in the production of the F2 generation does not exclude a treatment-related decrease in the number of primordial follicles after exposure to BPA PO during sensitive windows of pre- and postnatal development.

In developmentally exposed offspring, also the **pituitary gland** seemed to be affected by BPA PO exposure. Significantly decreased absolute and relative pituitary gland weights were recorded in high dose females from Cohort 1B (14% decrease in absolute and 14.8% in relative pituitary weight). Male offspring from cohort 1B showed very similar changes in pituitary weight, with a 14.8% decrease in absolute and 10% decrease in relative pituitary weights. Cohort 2B males showed a 39% decrease in absolute pituitary weight (-35% relative) and cohort 2B females showed a 20% decrease in absolute weight (-18.2% relative). In cohort 1A indeed absolute female pituitary weights in the high dose group were unaffected by exposure, but the relative weights were decreased by 8.2 %, and in cohort 1A males, a 9% decrease in absolute pituitary weights was seen. As adverse effects on were also seen on the pituitary glands of parental males and in the TG 408 study, this may not have been a developmental effect. In view of the low magnitude and lack of similar findings in Cohort 1A, the significant differences in pituitary weight in females from Cohort 1B were by the study report authors considered probably not to be related to the test item administration. The eMSCA does not share this conclusion, and finds that it is likely that pituitary weights had been decreased due to test substance administration. This conclusion is based on the fact that even though cohort 1B females were the only group with a statistically significantly lower pituitary weight than control, several indications of similar effect were observed in offspring from the other cohorts. No apparent decreases in pituitary weight were seen in P-generation females, cohort 3 males and females and cohort 2A females and males. However, the overall weight of evidence points in a direction of exposure related decreases on pituitary weight in both male and female rats exposed to BPA-PO at the highest exposure (360 mg/kg/day) and is supported by findings from the repeated dose toxicity study.

Animals from cohort 2A and 2B in the TG 443 study were examined for **developmental neurotoxicity**. The eMSCA finds that there were no behavioural results indicating developmental neurotoxicity. In both the auditory startle testing, the reactivity to manipulation or on different stimuli (Functional Observation Battery) and in the motor activity testing there were very high variations in the data but no tendencies towards any treatment related effects. In Cohort 2A, one significant finding was seen on brain morphometry. A 65% higher ***corpus callosum*** thickness was seen in high-dose males than in controls (986 µm±162 vs. 598µm ±77.5 in controls). In the study report this finding was described as ambiguous and not directly related to the test item because it was inconsistent across brain regions, and inconsistent across sex, across doses and across age. Based on the obtained results, the eMSCA finds that it cannot be excluded that the observed increase in corpus callosum thickness was treatment related, but it could also be a chance finding.

In cohort 2B, the ***striatum*** thickness was found to be lower in high-dose females than in controls. The evidence of neurotoxicity was named ambiguous in the study report, using the same argumentation as above, i.e. the difference was considered to be minimal (-17%), and no changes were noted in the low- and intermediate-dose females from Cohort 2B or in adult females from Cohort 2A. The eMSCA does not agree that a 17% decrease (5450.7± 468 vs. 6576.1± 885 in control) in this measurement is minimal and furthermore notes that cohort 2B males also showed a 13% decrease in this measure at the same age (though not statistically significant) (6043.8 vs. 6938.7+378 in controls).

Only one sample was examined, therefore no standard deviation in the high dose male group was derived. The fact that these differences in striatum thickness were no longer present when examined in adulthood (i.e. Cohort 2A) do not exclude a that treatment related effect could be present on day 22. Thus in the eMSCA's view, clear signs of **developmental neurotoxicity** were not seen, but treatment related effects on brain morphology parameters cannot be excluded.

No clear adverse **developmental immunotoxicity** effects were observed after exposure to BPA PO.

7.9.8. Hazard assessment of physico-chemical properties

Not assessed.

7.9.9. Selection of the critical DNEL(s) / DMEL(s) and / or qualitative / semi-quantitative descriptors for critical health effects

Not assessed.

7.9.10. Conclusions of the human health hazard assessment and related classification and labelling

The classification was determined in accordance with Regulation (EC) N°1272/2008.
There is no available clear evidence suggesting that the registered substance can be classified as a human reproductive toxicant. In the EOGRTS, no clear signs of developmental neurotoxicity or developmental immunotoxicity were observed. At the highest-dose and when compared with controls, there was an increased number of females in diestrus considered as test-item related, resulting in a prolongation of mean oestrous cycle duration. In addition, a lower fertility index was observed. This was however close to the lower value recorded in Historical Control Data, and therefore the registrant considered that a test-item treatment relationship was unlikely. These effects were only observed in Parental animals and not in animals from the F1 generation, therefore their relevance for the purpose of classification was considered as dubious. In the developmental toxicity / teratogenicity study performed in accordance with the OECD Testing Guideline 414, embryo/foetal toxicity associated with malformations was only observed in a context of excessive maternal toxicity and was therefore considered as a secondary effect to the systemic toxicity in the pregnant animals. There was conflicting evidence regarding the registered substance displaying an endocrine mode of action (see section 7.10), therefore no conclusion could be made regarding the endocrine disrupting properties of BPA PO. Therefore, it is now concluded by the eMSCA that the registered substance does not meet the criteria for classification as toxic to reproduction in accordance with Regulation (EC) N°1272/2008.

7.10. Assessment of endocrine disrupting (ED) properties

7.10.1. Endocrine disruption – Environment

Not assessed.

7.10.2. Endocrine disruption - Human health

The screening study on Grade 5 of BPA PO showed a concern for endocrine disruption in vivo. Further evaluation by QSAR model predictions on oestrogen receptor performed by the eMSCA indicated a potential concern that BPA PO may cause reproduction toxicity and endocrine-disrupting activity through binding of constituents of BPA PO to the oestrogen receptor.

Based on the results obtained during the screening, it was concluded that Grade 5 of BPA PO represented a greater concern than BPA 2PO, considering the high rate of oestrus cycle disorder induced by Grade 5 of BPA PO. However, Grade 5 of BPA PO can be regarded as a polymer under REACH, so it was ruled out as a test substance for the purpose of the EOGRTS. Since the outcome of the OECD 422 suggested that potential endocrine-disrupting properties could be related to higher degrees of propoxylation and therefore constituents with higher chain-length, Grade 4 of BPA PO was deemed as the most relevant test substance for this study by the eMSCA.
In addition, experimental testing for ER properties was requested by the eMSCA.

Stably Transfected Transactivation In Vitro Assays to Detect Oestrogen Receptor Agonists and Antagonists

An assumption was made that an endocrine mode of action could be related to the binding of some constituents of Grade 5 of BPA PO to estrogen receptor (ER). Therefore, experimental in vitro testing for ER properties was performed. Stably Transfected Transactivation in Vitro Assays to Detect Oestrogen Receptor Agonists and Antagonists were conducted on various BPA PO grades and compounds – BPA 2PO and Grades 3, 4 and 5 of BPA PO in accordance with the OECD Testing Guideline 455. The purpose was to identify if the test substances were ER agonists or antagonists and to confirm if ER properties – if any – increased with the degree of propoxylation of BPA PO compounds.
The ability of the four BPA PO compounds to establish signal activation or blocking of the estrogenic receptor was investigated in GLP compliant studies in accordance with the OECD Testing Guideline 455. Each of the four studies found the respective grade of BPA PO to be negative in both the ER agonist assay and ER antagonist assay when tested up to a concentration of 30 µM (Unpublished study report, 2018d-g). All four tests concluded that the test substances do not show any estrogenic or anti-estrogenic activity when tested in stably transfected human Oestrogen-α Transactivation Assay.

In vivo effects on the sex hormone system

Oestrous cyclicity disruptions were observed in the high dose females from the parental generation in the EOGRTS with BPO 4PO and in the TG 422 study with grade BPA 5PO, an increased rate of oestrous cycle disorder in females were observed at 500 mg/kg/day. As discussed previously (section 7.9.7.3), no effect on oestrous cyclicity was seen in the offspring, which somewhat reduces the significance of these findings in relation to this being a consistent adverse effect. A possible explanation for the apparent discrepancy between findings in parental females and offspring in the EOGRTS could be that a higher dose than the 360 mg/kg/day may be needed to elicit an effect on oestrous cyclicity. In the P-generation dams, oestrous cyclicity was measured shortly after the dose had been reduced from 540 mg/kg/day to 360 mg/kg/day. Hence, the high dose may have markedly affected the female endocrine/reproductive system, causing significant effects on oestrous cyclicity, which were not elicited by a dose of 360 mg/kg/day.

Mating, fertility and delivery seemed to be marginally affected in the parental generation in the EOGRTS. Since the high dose females had irregular oestrous cycles it is plausible that these irregularities could have affected the mating and fertility indexes. Reproductive development in female offspring may have been affected by BPA-PO exposure, when looking at the total **number of primordial follicles** on PCNA-stained

slides. In females from Cohort 1A, significant differences were observed between the control group and each of the test item treated groups.

All **prostate weights** group means (both absolute and relative) in high dose animals were smaller than in control animals, though most of them not statistically significantly. In addition, adverse histological effects were seen in 5/7 the high dose males of the TG 408 study. Since the other male reproductive organs did not seem to be affected, this does not point to an anti-androgenic mode of action, however compounds with an estrogenic mode of action have also been shown to be able to affect the prostate. Furthermore adverse effects on **pituitary gland** weigh and histopathology were observed, also indicating potential endocrine disrupting effects of the sex (and thyroid) hormone systems.

Some **sperm parameters** were affected in the TG 422 study with BPA 2PO. Impaired spermatogenesis was noted for males exposed to 250 and 500 mg/kg, with changes in sperm release seen in 2/7 (250 mg/kg bw/day) and 5/10 (500 mg/kg bw/day) males and spermatid retention in tubule stage X/XI observed in 2/5 (250 mg/kg bw/day) males. In the TG 422 study with BPA 5PO an effect on sperm parameters was also seen, as the count in stage XII was significantly different from controls in the 500 mg/kg bw/day group. No other stages were significantly affected, which in itself could indicate a chance finding. However, seen together with significantly affected sperm parameters in the TG 422 study with BPA 2PO, it could also indicate a real effect. In the TG 443 study, sperm quality was analysed in P-generation and F1 males, and no adverse effects were observed in any exposure group. It is hence plausible that the different grades of BPA PO affect sperm parameters differently.

No statistically significant effects were observed on measurements of **anogenital distance,** and analysis of **nipple retention** did not show any treatment related effects. There were some drawbacks of the used methods, which weaken the utility of the obtained results, in relation to interpretation of whether BPA-PO affected these early markers of endocrine disrupting effects.

When compared with controls, there were no statistically significant differences in the mean age of **balanopreputial separation** in males, **vaginal opening** in females or mean time to first oestrous after vaginal opening in females in Cohort 1A, 1B, 2A or 3. Also no consistent adverse effects on reproductive organ weights, apart from those listed above, were established.

In vivo effects on the thyroid hormone system

In the study reports for the TG 408 and TG 443 studies, many of the observed adverse effects on thyroid hormone weight and histopathology were not included in the study report summaries and generally in the TG 443 report, the thyroid hormone measurement were presented as non-dose related and non-adverse. In the eMSCA's view BPA PO exposure did cause dose-related adverse effects on the thyroid hormone system of rats exposed to higher doses of BPA PO, with a few exceptions, as specified below.

In the TG 443 study the effects were most pronounced in the P generation males, where both the mid and the high dose caused marked TSH increases (4777 and 5736 *vs.* 1934 pg/mL in controls) and T4 reductions (30.5 and 26.4 *vs.* 35.3 ng/mL in controls) (only statistically significant in the high dose group). Thyroid hormone levels were not measured in the P generation females, but a significant increase in adverse effects on the thyroid gland histopathology (follicular cell hypertrophy) was seen in both males (15/24) and females (5/22) from the parental generation exposed to the high dose of BPA PO. In parental males, also thyroid gland weights were increased. In the mid dose group the effects was significant when looking at relative thyroid weight (+14%) but not absolute (+8%). In the high dose group both absolute (+16%) and relative thyroid weights

(+24%) were significantly increased. In P-generation females, no signs of thyroid weight increases were seen.

In the TG 408 repeated dose toxicity study, follicular cell hypertrophy was seen in 5/7 males and 6/10 females treated at 500 mg/kg/day. Unfortunately, thyroid glands were not weighted in the TG 408 study and no hormonal measurements were performed. At the end of the treatment-free period minimal follicular cell hypertrophy was still seen in 1/3 males previously treated with 500 mg/kg/day, indicating that even after a month without treatment, the adverse effects had not yet completely disappeared.

In the male cohort 1A offspring that were sacrificed after 11 weeks of direct dosing, TSH levels were increased in the mid (+115%) and high (+107%) dose groups (3051 and 2937 *vs.* 1421pg/mL in controls). The effect was only statistically significant in the mid dose group. T4 levels were unaffected in the mid dose group, whereas high dose males showed a 12% decrease, which was not statistically significant. In cohort 1A females TSH levels were significantly increased in both mid (+99%) and high (+83%) dose groups (1085 and 996 *vs.* 544 pg/mL in controls), whereas no decreases in T4 levels were observed. Additionally in these animals, minimal to slight follicular cell hypertrophy was seen when histopathological assessments of the thyroid glands was performed. The incidence of this finding in both high dose males and females was 17/20, compared to 0/20 in controls. In males, a significant increase in relative thyroid weight was seen in the high dose (+11,8%) whereas the increase in absolute weight (7,6%) was not significant. In females, no significant changes in absolute or relative thyroid weight were seen. In cohort 1B thyroid glands were not weighed.

In Cohort 2A males, no statistically significant effects on thyroid weight were seen, but the mid dose did cause a 10.5% (9.7% relative) increase and the high dose caused an 8.5% increase (6.7% relative), compared to controls. In cohort 2A females, also no statistically significant changes were seen, even though mid dose females showed a 5.8% increase in thyroid weight (9.5% relative) and the high dose females showed a 9.9% increased (4.4% relative) thyroid weights.

In Cohort 2B and 3, i.e. animals killed just after weaning (cohort 2B) and after 30 days of direct exposure (cohort 3), no effects were seen on thyroid weights in either males or females. Also no significant differences between exposed and controls were seen on the levels of T4 and TSH in 22 day old male and female pups, which were not selected for any cohort (blood pooled within litter).

In conclusion, the thyroid hormone system of rats exposed to BPA PO seemed to be adversely affected. The changes were not apparent in all high-dose animals and the patterns were not always clear. The mode of action by which BPA-PO affects the thyroid hormone system is presently unknown. Induction of liver enzymes could be a possibility, as increased liver weights have been observed in all studies after BPA PO exposure but since T4 reductions were only rarely seen, other modes of action are in the eMSCA's view more likely. The observed decreases in pituitary weight and changes in pituitary histopathology could, together with the observed changes in TSH indicate that the central regulation of the HPT axis was affected. Based on the presently obtained results, it is not possible to say whether the observed pattern (i.e. adverse finding on thyroid gland weight and histopathology, increased TSH secretion, but only limited findings of T4 decreases), is indeed a true effect pattern. It could also be that the lack of T4 reductions more has to do with possible limitations in the methodology used for the T4 measurements.

It is in the eMSCA's view likely that the thyroid hormone system of pregnant dams was also affected by the high dose exposures of BPA PO. It is however very determining for the degree of adverse brain development in the offspring whether maternal T4 levels during pregnancy are severely decreased, and whether early postnatal T4 reductions in the offspring are marked. In the present study, there are unfortunately no results for any of these endpoints.

Developmental neurotoxicity was investigated in the offspring in the DNT cohort, and only sporadic effects were observed. It cannot with certainty be concluded, based on the available results whether these effects were either substance related or were related to developmental thyroid hormone disruption.

7.10.3. Conclusion on endocrine disrupting properties (human health)

Based on the data from the four OECD 455 *in vitro* studies, evaluating the estrogenic agonist and antagonist activity of 4,4'-Isopropylidenediphenol, propoxylated, Grade 2PO-5PO neither 2PO, 3PO, 4PO nor 5PO showed any estrogenic or anti-estrogenic activity when tested in a stably transfected human oestrogen receptor-α transactivation assay. *In vivo,* the results were not as clear, as some indication of endocrine disrupting effects were observed. The results are however not sufficient for clear identification as an endocrine disrupting chemical. The effects indicating potential reproductive toxicity, possibly mediated by an endocrine mode of action, were the following:
-Altered oestrous cyclicity in female rats exposed to doses of 540/360 mg/kg bw/day in the parental generation of the new TG 443 study, corroborating findings of similar effects at a dose of 500 mg/kg bw/day in the TG 422 study with BPA 5PO. Indications of altered oestrous were also seen after a treatment free period in females previously exposed to BPA 4PO at a dose of 500 mg/kg bw/day in the TG 408 study.
-Lower mating and fertility index in high dose females (540/360 mg/kg bw/day) from the parental generation in the TG 443 study, possibly related to these cycle irregularities.
-Decreased number of primordial follicles on PCNA-stained slides developmentally exposed females (cohort 1A). Significant differences were observed between the control group and each of test item treated groups.
-Consistent decreases in pituitary gland weights in high dose males and females from TG 443 study and changes in pituitary gland histology in TG 408.
-Changes in prostate weight in high dose males in TG 443 and in prostate histopathology all dose groups in the TG 408 study.
All other examined endpoints related to reproductive toxicity and endocrine disruption of the sex hormone system were not adversely affected.

The thyroid hormone system also seemed affected by BPA PO exposure, but the effects were not consistently seen for all thyroid relevant endpoints or all examined cohorts. Often increases in TSH levels and thyroid weight were observed together with adverse effects on thyroid gland histopathology (follicular hyperplasia), whereas T4 decreases were not always seen so the patterns were not always clear. The degree of T4 reductions during pre- and postnatal development, is probably very determining for the degree of adverse brain development of the offspring. Unfortunately, no T4 measurements on PD 4 pups were presented in the study report as it was not part of the OECD TG. Therefore, it cannot be determined whether these were affected. Some indications of developmental neurotoxicity were seen on brain morphometry, but not on behaviour. Whether these effects were related to potential thyroid hormone disruption during development cannot be dismissed.

Overall, there were also several endpoints of concern which were not adversely affected in the requested studies including nipple retention and anogenital distance which are considered to be sensitive endpoints for endocrine disruption. The eMSCA considers the results to be ambiguous as adverse effects were not seen across all endpoints, dose groups and cohorts and no clear adverse outcome pathway could be established.
The eMSCA also does not consider the adverse effects observed to be sufficiently severe to trigger further regulatory risk management measures at present.

7.11. PBT and VPVB assessment

7.11.1. PBT/vPvB criteria and justification

7.11.1.1. Persistence assessment

Biodegradation simulation studies are not available for the registered substance. In addition, no valid experimental information is available for readily biodegradability on the BPA PO derivatives with longer side chains than BPA 2PO since the results of the readily biodegradation study with BPA 5PO (UVCB) has been disregarded by the registrant(s). Consequently, no conclusion can be drawn on persistency potential of the registered substance.

Acoording to REACH, Annex XIII, a substance fulfills the criteria as persistent if at least one of the following conditions is met: a half-life in freshwater of above 40 days, a half-life in freshwater sediment of above 120 days or a half-life in soil of above 120 days.

According to the REACH PBT Guidance Document a substance fulfills the screening criteria for persistency if at least one of the two following combined predictions is achieved in Biowin:

- Biowin 2 gives a probability for “fast” degradation of < 0.5 corresponding to “slow” and Biowin 3 gives a rating for “complete” ultimate biodegradation of < 2.2 corresponding to at least months.
- Biowin 6 gives a probability < 0.5 and Biowin 3 gives a probability < 2.2

The lower propoxylated constituents (BPA 2PO and BPA 3PO) are predicted not to meet the screening persistency criterion wereas the higher constituents (BPA 4PO and above) are predicted to be persistent (see Epi Suite predictions in Table 30).

As supporting information, predictions from the PBT profiler are included in Table 30.

7.11.1.2. Bioaccumulation assessment

No relevant experimental information is available.

In the registration dossier a log Kow of 3.62 has been selected to characterize the registered substance. However, in a supporting study on BPA 5PO (UVCB) a Log P_{ow} of 3.11 - 5.99 was reported. In addition, QSAR estimates from KOWwin (v1.67) are from 3.79 to 5.06 for BPA PO derivatives ranging from 2PO to 9PO.

Therefore the registered substance is considered to fulfill the screening B criterion for log Kow.

The evaluating MSCA is of the opinion that the currently available information is insufficient to conclude on the bioaccumulation potential of BPA PO. Some of the constituents may have BCF values that exceed the CLP classification cut-off value of 500. In addition, although considered as unlikely based on the predicted BCF values in Table 30, it cannot be excluded that some of the longer PO derivates may exceed the bioaccumulation criterion of BCF = 2000.

The evaluating MSCA is therefore of the opinion that the standard information requirements of REACH, Annex IX, Section 9.3.2 may not be adequately addressed.

7.11.1.3. Toxicity assessment

No long-term NOECs for aquatic organisms are available (with the exeption of an EC10 for algae) and it cannot be assessed if the T criterion of NOEC < 0.01 mg/L has been fullfilled. The **screening** T criterion for EC50 < 0.1 is **not** fullfilled based on results from short-term studies with algae, daphnia and fish. It should be noted, however, that the tests have been conducted with either the UVCB BPA 5PO or the monoconstituent constituent BPA 2PO. According to ECOSAR the acute aquatic toxicity is increasing with the propoxyl chain length.

The evaluating MSCA notes that the registered substance could have endocrine disrupting effects that are not detected in the applied short-term studies for aquatic organisms. Therefore, it is possible that much lower effect values would be obtained in a relevant test that examines sensitive endocrine parameters.

Furthermore, since higher tier reproductive toxicity studies (i.e. OECD TG 414 and 443/416) and a 90 days repeated dose toxicity study (OECD 408) are lacking it is not possible to assess whether the critera for $T_{mamalian}$ are met or not.

7.11.2. Summary and overall conclusions on PBT or vPvB properties

The PBT/vPvB properties were not in the target of this substance evaluation. However, it seems that the PBT properties of the registered substance cannot be thoroughly evaluated at present due to lack of detailed information as outlined above.

Table 30.

PBT PROFILER				
Constituent	**Compartment**	**Predicted half-life (days)**	**Predicted BCF**	**Predicted chronic toxicity (mg/L)**
BPA 2PO_1_1	Water Soil Sediment	38 75 340	120	0.49
BPA 3PO_1_2	Water Soil Sediment	38 75 340	150	0.43
BPA 4PO_2_2	Water Soil Sediment	60 120 540	190	0.37
BPA 5PO_2_3	Water Soil Sediment	60 120 540	240	0.32
BPA 6PO_3_3	Water Soil Sediment	60 120 540	290	0.27

BPA 7PO_3_4	Water Soil Sediment	180 360 1,600	360	0.22
BPA 8PO_4_4	Water Soil Sediment	180 360 1,600	450	0.18
BPA 9PO_4_5	Water Soil Sediment	180 360 1,600	560	0.15

7.12. Exposure assessment

7.12.1. Human health

See below point 7.12.3.

7.12.2. Environment

See below point 7.12.3.

7.12.3. Combined exposure assessment

Exposures have been assessed for workers, consumers (one use, adults only) and the environment. Workplace and consumer exposures were assessed using the Advanced REACH Tool (ART) for inhalation exposures and EASE for dermal exposures. There are virtually no emissions of BPA(PO)n to the environment and environmental exposures were largely assessed qualitatively.

Five exposure scenarios have been identified:

ES1: Production of BPA (PO)n;

ES2: Use of BPA (PO)n in production of polyester resihn;

ES3: Use of polyester resin produced from BPA (PO)n in toner

ES4: Use of resin bound toner in copying/printing

ES5: Consumer use of toner containing trace quantities of BPA(PO)n in printers

As specified in the decision, the registrants were requested to update the CSR with information on personal protective equipment and documentation for the claim that risks to workers and consumers are adequately controlled and documentation for the claim that releases to the environment from recycling of paper are negligible.

Following this decision, the CSR has now been updated with the requested information and the concern has been clarified.

7.13. Risk characterisation

Following this decision, the chapter 10 of the CSR has now been updated with a specification of the RCRs which are < 0.01 and the concern is considered by the eMSCA to be clarified.

7.14. References

Ministry of Health, Labour and Welfare, Japan, 2010: Combined repeated dose toxicity study with reproduction/development toxicity test in rats (study report), Testing laboratory: Ministry of Health, Labour and Welfare, Japan, Report no: 06-119. Owner company; Ministry of Health, Labour and Welfare, Japan, Report date: Nov 4, 2010

Unpublished study report, 2011: COMBINED 28-DAY REPEATED DOSE TOXICITY STUDY WITH THE REPRODUCTION/DEVELOPMENTAL TOXICITY SCREENING TEST OF LIN10001 4 4 ISOPROPYLIDENEDIPHENOL PROPOXYLATED IN RATS BY ORAL GAVAGE (study report).

Unpublished study report, 2018a: 4,4'-Isopropylidenediphenol, propoxylated, Grade 4PO / 13-week toxicity study by the oral route (gavage) in rats followed by a 4-week treatment-free period (study report).

Unpublished study report, 2018b: Extended One-Generation Reproductive Toxicity Study By Oral Route (Gavage) In Rats (study report).

Unpublished study report, 2018c: 4,4'-Isopropylidenediphenol, propoxylated, Grade 4PO / Prenatal developmental toxicity study by oral route (gavage) in rats (study report).

Unpublished study report, 2018d: Evaluation of the Estrogenic Agonist and Antagonist Activity of 4,4'-Isopropylidenediphenol, propoxylated, Grade 2PO using the Stably Transfected Human Estrogen Receptor-α Transactivation Assay (hERα-HeLa-9903 Cell Line) (study report).

Unpublished study report, 2018e: Evaluation of the Estrogenic Agonist and Antagonist Activity of 4,4'-Isopropylidenediphenol, propoxylated, Grade 3PO using the Stably Transfected Human Estrogen Receptor-α Transactivation Assay (hERα-HeLa-9903 Cell Line) (study report).

Unpublished study report, 2018f: Evaluation of the Estrogenic Agonist and Antagonist Activity of 4,4'-Isopropylidenediphenol, propoxylated, Grade 4PO using the Stably Transfected Human Estrogen Receptor-α Transactivation Assay (hERα-HeLa-9903 Cell Line) (study report).

Unpublished study report, 2018g: Evaluation of the Estrogenic Agonist and Antagonist Activity of 4,4'-Isopropylidenediphenol, propoxylated, Grade 5PO using the Stably Transfected Human Estrogen Receptor-α Transactivation Assay (hERα-HeLa-9903 Cell Line) (study report).

7.15. Abbreviations

AC	Article category
AGD	Anogenital distance
BAF	Bioaccumulation factor
BCF	Bioconcentration factor
BPAPO	4,4'-Isopropylidenediphenol, propoxylated
CLP	Classification, labelling and packaging
CoRAP	Community rolling action plan
CSR	Chemical safety report
DIT	Developmental immunotoxicity
DNT	Developmental neurotoxicity
EC	Effect concentration
ECHA	European chemicals agency
eMSCA	Evaluating member state competent authority
EOGRTS	Extended one-generation reproductive toxicity study
ER	Estrogen receptor
ERC	Environmental release category
ES	Exposure scenario
GALT	Gut-associated lymphoid tissue
GLP	Good laboratory practice
K_{OC}	Organic carbon-water partition coefficient
K_{OW}	Octanol-water partition coefficient
HPLC	High-performance liquid chromatography
LD	Lethal dose
NOEC	No observed effect concentration
NOAEL	No observed adverse effect level
NR	Nipple retention
PBT	Persistent, bioaccumulative, toxic
PEC	Predicted environmental concentration

PNDT	Prenatal developmental toxicity
PNEC	Predicted no effect concentration
PC	Product category
PROC	Process category
QSAR	Quantitative structure-activity relationship
RCR	Risk characterization ratio
REACH	Registration, evaluation and authorisation of chemicals
SU	Sector end use
T3	Triiodothyronine
T4	Thyroxine
TPA	Tonnes per annum
TSH	Thyroid-stimulating hormone
US EPA	United States environmental protection agency
UVCB	Unknown or variable composition, complex reaction products or of biological materials