SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

Reaction mass of 3-[(diphenoxyphosphoryl)oxy]phenyl triphenyl 1,3-phenylene bis(phosphate) and tetraphenyl 1,3-phenylene bis(phosphate)

(EC number 701-337-2)

previously named

Tetraphenyl m-phenylene bis (phosphate)
(EC No 260-830-6)

Evaluating Member State(s): France

Dated: February 2022

Evaluating Member State Competent Authority

French Agency for Food, Environmental and Occupational Health Safety (ANSES) on behalf French Ministry of Environment
14 rue Pierre et Marie Curie
94701 MAISONS-ALFORT
France
Email: reach@anses.fr

Year of evaluation in CoRAP: 2020

Member State concluded the evaluation without any further need to ask more information from the registrants under Article 46(1) decision.

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

The Substance, Reaction mass of 3-[(diphenoxyphosphoryl)oxy]phenyl triphenyl 1,3-phenylene bis(phosphate) and tetraphenyl 1,3-phenylene bis(phosphate), with EC number 701-337-2 (below named as "RDP"), previously named Tetraphenyl m-phenylene bis (phosphate) (EC number 260-830-6, CAS RN 57583-54-7) was originally selected for substance evaluation in order to clarify concerns about:

- Suspected Reprotoxic
- Potential endocrine disruptor
- Suspected PBT/vPvB
- Consumer use
- Exposure of environment
- Exposure of workers
- High (aggregated) tonnage
- Wide dispersive use

During the evaluation additional concerns were identified, namely:

- Immunotoxicity
- Neurotoxicity

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Not applicable

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the Substance has led the evaluating Member State to the conclusion that, based on available data, the endocrine disruptive potential of RDP can neither be confirmed nor excluded (Table 1).

It is important to note that

- Data relevant to the intrinsic properties of RDP are expected, related to the ED potential of its impurity TPP (triphenyl phosphate, EC number 204-112-2), and
- A need for regulatory actions is under consideration for resorcinol, one of its metabolites.

These data and actions may indirectly result in risk management measures for RDP (eg. Classification as ED substance).

Therefore, it seems inappropriate at this stage to request complex animal studies for RDP, in particular for thyroid potential adverse effect to clarify possible ED properties. This conclusion will be reconsidered when the expected data on TPP and outcome of regulatory actions for resorcinol are available.

Table 1

CONCLUSION OF SUBSTANCE EVALUATION Conclusions	
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

4. FOLLOW-UP AT EU LEVEL

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

4.1.1. Harmonised Classification and Labelling

Not applicable

4.1.2. Identification as a substance of very high concern, SVHC (first step towards authorisation)

Not applicable

4.1.3. Restriction

Not applicable

4.1.4. Other EU-wide regulatory risk management measures

Not applicable

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

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

The current conclusion shall be reconsidered when the expected data on impurities and the results of regulatory actions for metabolites become available. Indeed, two processes are still ongoing:

- For TPP (impurity of RDP, EC number 204-112-2), a Substance evaluation is ongoing, in particular to investigate its ED properties.
- For resorcinol (metabolite of RDP, EC number 203-585-2), an SVHC identification due to its ED properties for human health is under discussion and a Substance evaluation is ongoing to generate data on its ED properties for the environment.

The result of these processes may impact the need for a regulatory follow-up for RDP, i.e. the need to apply risk management measures or to further investigate the ED properties of RDP.

5.2. Other actions

Not applicable.

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

Not applicable.

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

The Substance, Reaction mass of 3-[(diphenoxyphosphoryl)oxy]phenyl triphenyl 1,3-phenylene bis(phosphate) and tetraphenyl 1,3-phenylene bis(phosphate), with EC number 701-337-2 (below named as "RDP"), previously named Tetraphenyl m-phenylene bis (phosphate) (EC number 260-830-6, CAS RN 57583-54-7) was originally selected for substance evaluation in order to clarify concerns about:

- Suspected Reprotoxic
- Potential endocrine disruptor
- Suspected PBT/vPvB
- Consumer use
- Exposure of environment
- Exposure of workers
- High (aggregated) tonnage
- Wide dispersive use

During the evaluation additional concerns were identified, namely:

- Immunotoxicity
- Neurotoxicity

Table 4

EVALUATED ENDPOINTS Endpoint evaluated	Outcome/conclusion
Suspected Reprotoxic	Concern for fertility and *in utero* development refuted. Concern unresolved. Delay in post-natal growth and its origin to be clarified if no regulatory action based on TPP or resorcinol is taken.
Potential endocrine disruptor	Concern unresolved. Concern for thyroid and adrenals disruption to be clarified at a later stage, in particular if no regulatory action based on TPP or resorcinol is taken.
PBT	Concern refuted. RDP seems not to rapidly biodegrade, not meeting the P/vP and B/vB criteria, nor the T criteria
Consumer use	Concern confirmed. Exposure of general population, including children, confirmed by available literature.
Exposure of environment	Concern unresolved.
Exposure of workers	Concern confirmed. Exposure of workers is confirmed to be relevant based on RDP uses but level of exposure not further investigated

High (aggregated) tonnage	Concern unresolved.
Wide dispersive use	Concern unresolved.
Immunotoxicity	Concern refuted. No further action.
Neurotoxicity	Concern refuted. No concern for a direct neurotoxic potential. Concern unresolved. Neurodevelopmental potential in relation to thyroid disruption potential to be clarified if no regulatory action based on TPP or resorcinol is taken.
Additional endpoints	
Environmental fate	See below section 7.7 for details
Environmental hazards	See below sections 7.8.1,to 7.8.5 for details
Toxicokinetics	See below section 7.9.1 for details
Repeated dose toxicity	See below section 7.9.4 for details

7.2. Procedure

The substance, Tetraphenyl m-phenylene bis (phosphate) (EC No 260-830-6, CAS RN 57583-54-7) was included in 2016 in the manual screening process, then evaluated in 2016 during the French national endocrine disruptor strategy.

From 2013 to 2018, the Substance with EC No 260-830-6 (CAS RN 57583-54-7) was assessed in several compliance checks and data were requested on:

- The standard information required in the Annex VII (partition coefficient n-octanol/water method) (CCH-D-0000002994-63-05/F).
- *In vitro* gene mutation study in mammalian cells (Annex VIII, Section 8.4.3) (CCH-D-0000002994-63-06/F).
- SID information (name in the IUPAC nomenclature with EC and/or CAS entry) (CCH-D-21143607 52-49-01/F).
- Toxicological tests: Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2) and Pre-natal developmental toxicity study (Annex X, Section 8.7.2) (CCH- D-21143607 52-49-01/F).
- Standard information required in Annexes I and VI on classification and labelling, identification of PNEC, exposure assessment and risk characterization for the environment and human health (CCH-D-2114408319-50-01/F).

In March 2020, Tetraphenyl m-phenylene bis(phosphate) (EC No 260-830-6, CAS RN 57583-54-7) was included in the Community rolling action plan (CoRAP) for substance evaluation to be evaluated due to initial ground of concerns related to reproductive toxicity, high (aggregated) tonnage, potential endocrine disruptor, environmental toxicity and wide dispersive use.

In June 2020, the SID information was updated by several registrants: due to a change of some composition of the substance, there was a change of substance identity with a new EC number for RDP >1000t: EC number 701-337-2, with a new name: Reaction mass of 3-[(diphenoxyphosphoryl)oxy]phenyl triphenyl 1,3-phenylene bis(phosphate) and tetraphenyl 1,3-phenylene bis(phosphate) (or RDP).

After discussion with ECHA, it was agreed that the RDP substance listed on the CoRAP (Tetraphenyl m-phenylene bis (phosphate), EC No 260-830-6; CAS RN 57583-54-7) was the same substance than the substance registered with the EC number 701-337-2.

During the evaluation period (until March 2021), FR-MSCA communicated with the lead registrant to obtain some toxicological and ecotoxicological data, and on 22 October 2020, Fr-MSCA met the lead registrant to clarify some toxicological data.

The substance was discussed with the experts of the PBT and ED EGs, respectively on 26 October 2020 and on 17 November 2020.

In December 2020, FR-MSCA consulted ECHA on the best strategy forward: two evaluation processes are ongoing for both TPP (impurity, EC number 204-112-2) and resorcinol (metabolite of RDP, EC number 203-585-2); hence FR-MSCA wanted to suspend the RDP evaluation until receipt of the TPP data, planned in March 2021. ECHA argued to conclude the evaluation and to consider re-opening the evaluation of RDP when all needed information is available: the additional information (OECD TG 234 on TPP and OECD TG 241 on resorcinol) can be considered as "change of circumstances" which can justify putting the substance back onto the CoRAP (Article 47(1) REACH).

On 4 January 2021, FR-MSCA informed ECHA that it intends to conclude on the evaluation of the RDP, but reserves the right to resubmit the RDP for evaluation when the impurity (TPP) and metabolite (Resorcinol) data are available.

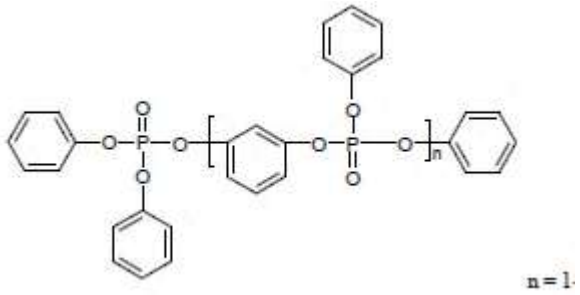
7.3. Identity of the substance

Table 5

SUBSTANCE IDENTITY	
Public name:	Tetraphenyl m-phenylene bis(phosphate)
EC number:	260-830-6 / 701-337-2
EC name:	Tetraphenyl m-phenylene bis(phosphate)
CAS number:	57583-54-7
IUPAC name:	Reaction mass of Tetraphenyl resorcinol diphosphate n=1 and Tetraphenyl resorcinol diphosphate n=2
Index number in Annex VI of the CLP Regulation:	None
Molecular formula:	$C_{30}H_{24}O_8P_2$ to $C_{102}H_{78}O_{32}P_8$
Molecular weight range:	574.45 where n=1 1070.79 (n=2)
Synonyms:	tetraphenyl 1,3-phenylene bis(phosphate) Resorcinol bis-diphenylphosphate (RDP); Resorcinol bis (biphenylphosphate); Tetraphenyl resorcinol diphosphate; Reaction mass of 3-[(diphenoxyphosphoryl)oxy]phenyl triphenyl 1,3-phenylene bis(phosphate) and tetraphenyl 1,3-phenylene bis(phosphate) (EC 701-337-2) Trade name: Reofos® RDP

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

Structural formula where n=1-2:



The compositions submitted by the registrants are considered as multiconstituent according to REACH guidance for identification and naming of substances (see the confidential annex). Analytical information are provided (UV/VIS, IR, NMR and GC chromatograms) to confirm the compositions and the structure of substances of each submitter.

Multiconstituent/UVCB substance/others

Table 6

Constituent Constituents	Typical concentration	Concentration range	Remarks
Tetraphenyl 1,3-phenylene bis(phosphate), where n=1 (EC no 260-830-6)	72	60-74	$C_{30}H_{24}O_8P_2$
Tetraphenyl 1,3-phenylene bis(phosphate), where n=2 (CAS RN 98165-92-5)	17	15-25	$C_{42}H_{33}O_{12}P_3$
Triphenyl phosphate (EC no 204-112-2, CAS RN 115-86-6)	Confidential	Confidential	$C_{18}H_{15}O_4P$

7.4. Physico-chemical properties

Table 7

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES Property	Value
Physical state at 20°C and 101.3 kPa	Value used for SEV: clear colourless to light yellowish liquid
Melting / freezing point	Value used for SEV: < -13 °C Melting point was determined in accordance with the test method OECD TG 102.
Boiling point	Value used for SEV: > 400 °C Boiling point was determined in accordance with the test method OECD TG 103.
Relative density	Value used for SEV: 1.306 at 20 °C Relative density was determined in accordance with the test method OECD TG 109.
Granulometry	Not relevant as RDP is a liquid

Vapour pressure	Value used for SEV: 2.59.10-3 Pa at 20 °C (supporting data) A Vapour pressure of 2.59.10-3 Pa at 20 °C was determined according to the test procedure OECD TG 104 (Spinning rotor gauge method) and GLP requirements. However as the measurement was made on the test mixture, with the test procedure OECD TG 104, it is not possible to identified what is really measured in the mixture for vapour pressure.
Partition coefficient n-octanol/water (Log Kow)	Value used for SEV: Supportive data Triphenyl phosphate (TPP): Log Kow: 4.07 n=1 : Log Kow: 5.51 n=2 and more: Log Kow: > 6.5 Partition coefficient was determined according to the test procedure OECD TG 117 (EU test method A.8; HPLC method) and GLP requirements. However for the determination of the partition coefficient n-octanol/water described in EU test method A.8 is not applicable to surface active material.
Water solubility	Value used for SEV: 10738 ± 145 µg/L at 20 °C (TPP): n=1: 8.91 ± 1.3 µg/L at 20 °C n=2 and more: < 3.33 µg/L at 20 °C Water solubility was determined according to the test procedure OECD TG 105 and GLP requirements.
Surface tension	Value used for SEV: 48.9 mN/m at 22.3 °C Surface tension was determined accoding to the test procedure EU test method A.5. The mixture is surface-active.
Flammability	Value used for SEV: non flammable The flashpoint of RDP was determined in accordance to a similar to EU method A.9 using the closed cup method. The flashpoint was found to be > 225 °C.
Explosive properties	Value used for SEV: non explosive According to the REACH guidance, chapter R7.A, RDP does not contain any chemical groups associated with explosive properties. Thus, according to REACH Annex VII, column 2, a study does not need to be conducted.
Oxidising properties	Value used for SEV: non oxidising According to the REACH guidance, chapter R7.A, a study on the oxidising properties does not need to be conducted as RDP does not contain any chemical groups associated with oxidising properties (Table R.7.1-29).
Stability in organic solvents and identity of relevant degradation products	In accordance REACH guidance, chapter R7.A, a test on the stability in organic solvents is not necessary because this stability is not considered to be critical based on chemical structure and experience in use.
Dissociation constant	According to the REACH guidance, chapter R7.A, a study on the dissociation constant of RDP is not required due to a lack of relevant functional groups.
Viscosity	Value used for SEV: 600 cP at 25°C Viscosity of the substance was determined according to OECD TG 114 using a rotational viscometer.

7.5. Manufacture and uses

7.5.1. Quantities

Table 8

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 9

USES	Use(s)
Uses as intermediate	
Formulation	PROC 2: Use in closed, continuous process with occasional controlled exposure PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) PROC 14: Production of preparations or articles by tabletting, compression, extrusion, palletisation PROC 21: Low energy manipulation of substances bound in materials and/or articles PROC 24: High (mechanical) energy work-up of substances bound in materials and/or articles PC 32: Polymer preparations and compounds Uses at industrial sites ERC2: Formulation into mixture ERC3: Formulation into solid matrix
Uses at industrial sites	PROC 1: Use in closed process, no likelihood of exposure PROC 3: Use in closed batch process (synthesis or formulation) PROC 4: Use in batch and other process (synthesis) where opportunity for exposure arises PROC 5: Mixing or blending in batch processes for formulation of preparations and articles (multistage and/or significant contact) PROC 6: Calendering operations PROC 7: Industrial spraying PROC 8b: Transfer of substance or preparation (charging/discharging) from/to vessels/large containers at dedicated facilities PROC 9: Transfer of substance or preparation into small containers (dedicated filling line, including weighing) PROC 10: Roller application or brushing PROC 13: Treatment of articles by dipping and pouring PROC 14: Production of preparations or articles by tabletting, compression, extrusion, palletisation PROC 21: Low energy manipulation of substances bound in materials and/or articles PROC 24: High (mechanical) energy work-up of substances bound in materials and/or articles PC 32: Polymer preparations and compounds PC 34: Textile dyes, and impregnating products

	ERC4: Use of non-reactive processing aid at industrial site (no inclusion into or onto article) ERC5: Use at industrial site leading to inclusion into/onto article ERC6b: Use of reactive processing aid at industrial site (no inclusion into or onto article)
Uses by professional workers	PROC 21: Low energy manipulation of substances bound in materials and/or articles
Consumer Uses	PC 32: Polymer preparations and compounds
Article service life	AC 1: Vehicles AC 2: Machinery, mechanical appliances, electrical/electronic articles AC 5: Fabrics, textiles and apparel AC 13: Plastic articles

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

No harmonized classification

7.6.2. Self-classification

- In the registration(s)*:* \
- The following hazard classes are in addition notified among the aggregated self-classifications in the C&L Inventory*:*

Table 10

Hazard class category code(s)	Hazard statement code(s)	Number of notifiers
Not classified	/	28
Aquatic Chronic 3	H412	69
Aquatic Chronic 2	H411	32

7.7. Environmental fate properties

7.7.1. Degradation

7.7.1.1. Abiotic degradation

The available information suggest that Fyrolflex RDP is hydrolytically stable. The rate of hydrolysis has been determined in OECD TG 111, and is found to be dependent of temperature and pH.

Table 11

Method	Results	Remarks	Reference
according to OECD TG 111 (Hydrolysis as a Function of pH) single samples were taken in triplicate at each pH/temperature/time combination and analysed method not reported	Half-life (DT50): t1/2 (pH 4): 11.3 d at 20°C; t1/2 (pH 7): 17 d at 20°C; t1/2 (pH 9): 21.2 d at 20°C; t1/2 (pH 4): 54.7 d at 10°C; t1/2 (pH 7): 19 d at 10°C; t1/2 (pH 9): 32 at 10°C; Transformation products: not measured	2 (reliable with restriction) key study experimental result Test material (EC name): Fyroflex RDP	Kendall TZ, Nixon WB, 2000

The hydrolysis did not strictly follow a pseudo-first order kinetics, but reached a plateau, suggesting an equilibrium process between parent and degradation product(s).

No information is available regarding the phototransformation and photolysis of RDP in air, water or soil. Several studies have shown that aryl phosphate can undergo photolytic degradation using UV radiation. However, as the amount of UV radiation reaching the earth's surface is small, the significance of these mechanisms to the behaviour in the environment is considered as being very limited.

7.7.1.2. Biotic degradation

The use of EPIWeb v4.1 to predict the potential biodegradation of RDP is detailed in Table 12 (parameters used in the model are detailed in sections 7.3 and 7.4).

Table 12 - Biodegradation prediction of RDP by EPIWeb v4.1.

EPI Suite			
Biowin 1	1,6143	Fast	
Biowin 2	1	Fast	
Biowin 3	2,3252	Fast	Weeks-Months
Biowin 4	3,9692	Fast	Days
Biowin 5	-0,4902	Not fast	
Biowin 6	0,0001	Not fast	
Biowin 7	0,4725	Not fast	
Ready Biodegradation Prediction	NO	Biowin 3 is weeks but Biowin 5 <0,5	

Two screening studies are available in the CSR and are summarised below.

Table 13: Screening tests for biodegradation in water

Method	Results	Remarks	Reference
Biodegradation in water: ready biodegradability: activated sludge, domestic, non-adapted (aerobic) according to OECD TG 301D (Ready Biodegradability: Closed Bottle Test) ; according to EU Method C.6 (Degradation: Chemical Oxygen Demand) ; according to ISO 10707 (1994)	% Degradation of test substance: 61 after 28 d (O_2 consumption)	1 (reliable without restriction) key study experimental result Test material (EC name): Fyrolflex RDP Form: liquid: viscous	Unpublished report, 2007
Biodegradation in water: ready biodegradability: activated sludge, domestic, non-adapted (aerobic) according to OECD TG 301D (Ready Biodegradability: Closed Bottle Test) This test was performed according to slightly modified EEC, OECD and ISO Test Guidelines (OECD, 1992; EEC 1984; ISO, 1994). The test was modified to allow prolonged measurements.	Poorly biodegradable % Degradation of test substance: 37 after 28d (66 bafter 56 days, O_2 consumption)	1 (reliable without restrictions) key study experimental result Test material (EC name): Fyrolflex RDP Form: liquid: viscous	Unpublished report, 1996b

The biodegradation of the test substance was studied in a Closed Bottle test according to the slightly modified OECD (OECD TG 301D), EU and ISO guidelines under GLP

(Unpublished report, 2007, Reliability 1, key study). According to the CSR, RDP was found to be readily biodegradable (61% degradation in 28 days). Nevertheless, the 10-day window quality criteria was not met during the assay. Indeed, after 8 days, 10% of degradation was noticed and 51% degradation was achieved after 18 days. All other quality criteria were met.

In a prolonged Closed Bottle test using sludge from WWTP treating domestic waste water, the degradation rate was lower (37% at 28 days) but after 56 days the mineralisation had reached 66% (Unpublished report, 1996). Again, the 10-day window criteria was not met.

In literature, a study by Jurgens et al., 2014, investigated the mineralization and primary biodegradation of of RDP and TPP by activated sludge based on the OECD TG 310 in triplicate. TPP (purity of 99%) and RDP (purity of 80%, technical mixture) individual stock solutions were prepared in either methanol or acetonitrile (ACN). Briefly, the solutions were prepared to give a final concentrations of 2 and 20 mg/L in glass serum bottles and allowing the methanol to evaporate overnight. Mineral medium (60 mL) and activated sludge (to give 30 mg/L total suspended solid (TSS)) were added the next day. Toxicity tests were performed in parallel similarilly to those in the mineralisation tests but in addition contained glucose (50 mg/L). Controls were also performed concomitantly to test for abiotic degradation with no inoculum and were sterilised with 1 mM sodium azide. The vessels were closed, the head space overpressure was set at approximately 700 mbar with synthetic air and the bottles were incubated at room temperature in the dark. Mineralisation was monitored by analysing the CO2 production every 3–4 d. Blank CO2 production by the inoculum (activated sludge without any addition) was substracted from the CO2 production in the treatments. The primary biodegradation consisted of 25 mL mineral medium in 100 mL-erlenmeyer flasks inoculated with diluted secondary sludge to give a TSS of 100 mg/L and a final concentration of solution of 200µg/L. In addition, toxicity tests were conducted to monitor the vitality of the sludge microorganisms during the incubation. These were prepared similarly as the biodegradation treatments, but additionally contained 200 mg/L benzoic acid as substrate for the bacteria. The abiotic incubations were sterilised with 1 mM sodium azide which was spiked weekly to maintain a sterile environment. The treatments were incubated at room temperature in the dark. Regarding mineralisation, CO2 yields obtained at 2 mg/L could not be distinguished from those observed in blank incubations. After 28 d, 18.0 ± 10.5 % mineralisation of RDP was achieved, indicating that this compound is not readily biodegradable. For TPP, 99.0 ± 24.3% mineralisation was achieved after 28 d, indicating that it is ready biodegradable. No mineralisation was recorded in the sterile control, indicating that mineralisation occurred only trough microbial activity. Mineralisation of glucose in the presence of TPP was 142 ± 14.6% indicating no toxicity of TPP and that TPP is most likely acting as an additional carbon source. For RDP, glucose mineralisation was 61.6 ± 2.0 % compared to 64.4 ± 1.2% in the reference, indicating that RDP was not toxic.

Regarding primary biodegradation, RDP was completely removed in the biodegradation incubations within 4 d (biodegradation rate constant 0.80 ± 0.08 d, DT50 < 1 d), while abiotic degradation was significantly slower (rate constant 0.03 ± 0.01 d, DT50 =18d) ($p < 0.001$). The rapid removal of RDP in the primary biodegradation study is in contradiction with slow mineralisation observed in the mineralisation tests (Jurgens et al., 2014). This suggests that poorly degradable transformation products may have accumulated in the biodegradation incubations. For TPP, rapid removal was observed with complete removal occurring within 7 d (DT50 of 2.8 d). As was observed for mineralisation, TPP removal was significantly slower in sterilised sludge (complete removal after 28 d and DT50: 8 days). For both RDP and TPP, diphenyl phosphate (DPP) was identified in the differents experiments. The DPP released during biotic degradation of TPP was completely removed during the experiment, whereas it accumulated in the sterilised abiotic incubations, indicating that the removal of TPP was due to hydrolysis in the sterile system. Both abiotic and microbial degradation could contribute to the conversion of TPP to DPP by hydrolysis of a phosphate ester linkage, but in the case of biotic degradation, DPP is degraded further by the biota present in the sludge. As was observed for TPP, DPP was formed when RDP was degraded and reached its maximum concentration as the RDP concentration fell below

the LOQ (not provided). DPP was not completely removed by biodegradation, but persisted at low levels (ca. 40 nM). No other degradation products could be identified in these incubations (could be due to limitations of the instrumentation used). As was observed for TPP, the DPP that is formed from RDP in sterilised sludge seems to accumulate as end product. The author precised that the rapid primary biodegradation but slow mineralisation of RDP implies that significant accumulation of transformation products (or intermediates) occurs. Due to the lack of mineralisation of RDP, it should not be considered ready biodegradable, despite of its rapid primary biodegradation.

7.7.1.3. Simulation tests (water and sediments)

No relevant information is available as the CSR considered that the substance is readily biodegradable.

7.7.1.4. Summary and discussion of biodegradation in water and sediment

Two guideline studies on the ready biodegradability of RDP were available in the CSR and one was retrieved from the literature. The biodegradation of the substance was tested according to OECD TG 301D and OECD TG 310. Tests used non-adapted activated sludge as inoculum. At termination of the test after 28 days of inoculation, the detected degradation rate was diverging depending on the study considered. In the OECD TG 301D, RDP was degraded to 61% after 28d but without meeting the 10-days windows criteria (Unpublished report, 2007). In an OECD TG 310, RDP was not considered as readily biodegradable as degradation reach 18% after 28 days (Jurgens et al., 2014). In an extended OECD TG 301D, degradation of RDP was 66% after 56 days (Unpublished report,1996). A primary biodegradation experiment of RDP was carried out with activated sludge and allowed disappearance of the parent compound (RDP) and appearance of metabolites within 4 days (biodegradation rate constant 0.80 ± 0.08 d, DT50 < 1 d) (Jurgens et al., 2014).

Thus, in view of elements on potential degradability, facilitated biodegradability and longer term biodegradation, RDP does not appear to meet the P/ vP criteria according to the EG PBT expert group of ECHA. However, RDP does not meet the conditions for readily degradability and could be considered non-persistent, provided that the primary degradation products themselves exhibit neither persistence nor toxicity.

7.7.2. Environmental distribution

Matsukami et al., 2017, investigated the concentrations of phosphorus flame retardants (PFRs) in surface soils and river sediments from an informal electronic waste (e-waste) processing area in Bui Dau (Hung Yen Province, northern Vietnam) for the period 2012-2014 (see 7.8.2 for soil data). In January 2012 sediment samples were collected from a river from upstream (n=1), near the e-waste processing workshop sites (n=3), and downstream (n=4). The samples collection was perfomed again in 2013 and 2014, leading to a total of 24 sediment samples. Samples were analysed by LC-ESI-MS/MS, LC-APPI-QTOF-MS and GPC. RDP median concentration in the upstream river site increased from < LOD (0.7 ng/g) to 2.3 ng/g dw (2012 to 2014), the e-waste processing site RDP median concentration increased from 4.6 to 330 ng/g dw and in downstream river sites from 3.2 to 23 ng/g dw. TPP median concentration was quite stable in upstream river site from 2012 to 2014 (<3 to 4.4 ng/g dw), increased at e-waste processing site from 7.3 to 200 ng/g dw and at downstream river sites from <3 to 36 ng/g dw. The medians concentration for RDP and TPP in river sediments collected from the downstream sampling points increased by up to 7 and 12 folds, respectively. These results indicate that the target PFRs in river sediments from the e-waste-processing workshop sites gradually diffused downstream under the influence of the river current. The authors suggest that these compounds might be adsorbed by and carried with suspended solids in the river water. The authors then determined the environmental emission of oligomeric PFRs and observed between 2013 and 2014 and observed that the ratio for degradation products and technical formulation

of RDP suggest an increase in median concentrations of HP-DPHP (3-hydroxyphenyl diphenyl phosphate) that arises from instability of RDP.

Matsukami et al., 2015, investigated the concentrations of organophosphorus flame retardants (OPFRs) in surface soils and river sediments from an informal e-waste-processing area in Bui Dau (Hung Yen Province, northern Vietnam) (see 7.8.2 for soil data). They collected river sediment samples from a river from upstream (n=1), near the e-wasteprocessing workshop sites (n=3), and downstream (n=4) in January 2012. Samples were analysed by LC-ESI-MS/MS, LC-APPI-QTOF-MS and GPC. RDP concentration in the upstream river site was <LOQ (0.7 ng/g dw), comprised between 1.7 to 78 ng/g dw (n= 3/3) at the e-waste processing site and comprised between <LOQ and 4.4 ng/g dw (n= 2/4) at downstream river sites. TPP concentration in the upstream river site was <LOQ (3 ng/g dw), comprised between 4.3 to 38 ng/g dw (n=3/3) at the e-waste processing site and comprised between <LOQ and 4.1 ng/g dw (n=1/4) at downstream river sites. was quite stable in upstream river site from 2012 to 2014 (<3 to 4.4 ng/g dw), increased at e-waste processing site from 7.3 to 200 ng/g dw and at downstream river sites from <3 to 36 ng/g dw.

Rodil et al., 2005, investigated the occurrence of OPFRs in 24h composite samples of the influent, primary effluent, and the tertiary effluent of a municipal WWTP collected in August 2004 with LC-ESI-MS/MS. RDP was never detected in composite samples (LOQ of 73 ng/L).

7.7.3. Bioaccumulation

7.7.3.1. Aquatic bioaccumulation

The estimated log Kow (partitioning coefficient) of the substance is between < -1.02 and > 6.50. For the estimation of BCF, the value used for the log Kow is 5.5, based on a read-across estimate with similar aryl phosphates performed by UK in 2009 (Brooke et al., 2009). The estimate with EPIWeb v4.1. gave an estimated log Kow of 7.41. Another log Kow value was estimated for the commercial polymeric substance, of being 4.93 (US EPA, 2018). Despite the incertitude raised by these variations, these different values are all indicative of a potential bioaccumulation of RDP.

Using EPIWeb v4.1 to estimate the potential BCF value fr RDP with these different log Kow value led to the results reported in Table 14.

Table 14

		US EPA (commercial polymeric substance)	**CSR**	**EPISuite**
	Log Kow	4,93	5,5	7,41
BCF Fish	*with biotransformation*	124,4	295,8	1256
	without biotransformation	6986	15560	7228

There is an alert for the potential bioaccumulation of RDP when no biotransformation occurs, based on structural estimation. This is also reflected in modelisation from the UK Environment Agency (Brooke et al., 2009); for earthworm, were a log Kow of 5.5 give a BCF value of 3796 L/kg and a value of more than 308 000 L/kg for a log Kow of 7.41.

The sole data available in the CSR is based on a read-across with structuraly close aryl phosphate (Table 15). This value is higher than the previsouly described estimated value obtained with EPIweb (a log Kow of 5.5 will normally led to a estimated BFC of 296).

Table 15: Studies on aquatic bioaccumulation

Method	Results	Remarks	Reference
Read-across based on grouping of substances	Bioaccumulation factor: BCF: 969 L/kg Elimination: not specified; Lipid content: Transformation products:	2 (reliable with restriction) key study Test material (EC name): read across based on grouping of substances	Brooke DN, Crookes MJ, Quarterman P, Burns J, 2009

Data used to derive missing value of RDP are presented in Table 16 (Brooke et al., 2009).

Table 16

Phosphate ester	Property								
	Measured vapour pressure at 20°C (Pa)	Measured water solubility at room temperature (mg/l)	Measured Log K_{ow}	Measured BCF (l/kg)	Long-term NOEC for aquatic organisms (mg/l)			EPI Estimates	
					Fish	Invertebrates	Algae	Vapour pressure at 25°C (Pa)	Log K_{ow}
Triphenyl phosphate	1.2×10^{-3}	1.9	4.63	420	0.037		0.1	2.8×10^{-5}	4.70
Trixylenyl phosphate	[4.7×10^{-4}][a]	0.89	5.63	1,300-1,900				2.7×10^{-6}	7.98
Tricresyl phosphate	3.5×10^{-5}	0.36	5.11	800	0.00032	0.1	0.32	3.4×10^{-6}	6.34
Cresyl diphenyl phosphate	3.3×10^{-5}	2.6	4.51	200				1.4×10^{-5}	5.24
Tris(isopropylphenyl) phosphate	2.3×10^{-6}				0.024[b]	0.006[b]		2.7×10^{-6}	9.07
Isopropylphenyl diphenyl phosphate	9.5×10^{-6}	2.2	5.30	[7,266][a]	0.024[b]	0.006[b]		5.3×10^{-6}	6.16
Tertbutylphenyl diphenyl phosphate	7.8×10^{-5}	0.04-3.2	5.12	778	0.093	0.010		3.5×10^{-6}	6.61
2-Ethylhexyl diphenyl phosphate	3.4×10^{-4}	0.38-1.9[c]	5.73	934	0.021	0.018		2.5×10^{-5}	6.30
Isodecyl diphenyl phosphate	[3.8][a]	0.03-0.75[c]	5.44	335	0.057	0.004		6.3×10^{-6}	7.28
Tetraphenyl resorcinol diphosphate		0.69				>0.064		2.7×10^{-6}	7.41

Notes: a) These values are uncertain (see main risk assessment reports) and have not been included in the estimation analysis.
b) Assumes these two products have similar toxicity.
c) Revised solubilities used in the individual risk assessment reports, the values here are used in the estimation analysis.

This estimate is based on a linear regression (Figure 1 below) using available BCF data for other aryl phosphates. The modelisation and estimate of BCF of RDP performed by the UK Environment Agency seem of good quality, with a good fit of the linear regression, despite a quite low R^2 value.

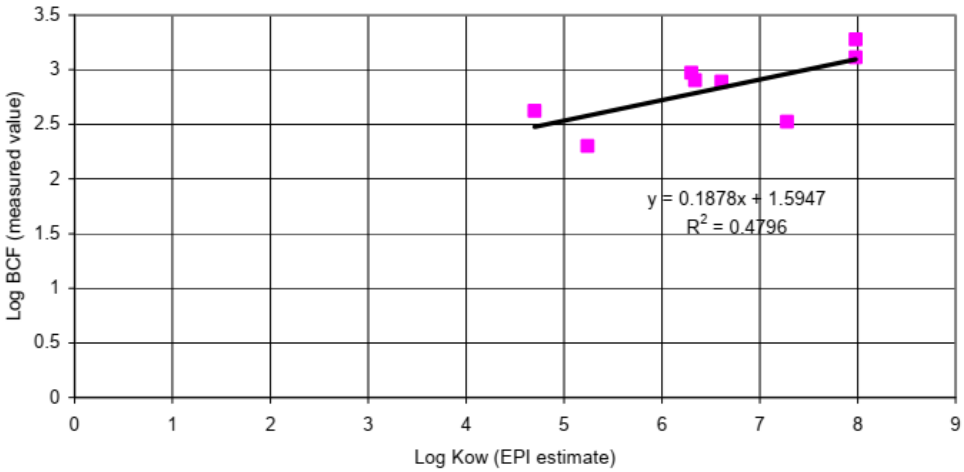


Figure 1: Linear regression

The linear regression was made with estimated log Kow (EPI suite estimation) vs experimental log Kow probably to avoid under estimating of what can be observed in experimental tests.

Two studies on the potential bioaccumulation of RDP are available in the literature:

- Zhao et al., 2019, investigated the bioaccumulation and trophic transfer of RDP in sediment, water and food web (plankton, invertebrates, and fishes) collected in August 2014 from Taihu Lake, China. Sixty pairs of water and sediment samples were collected. Among them, 39 were collected from the northwestern area of the lake (including Zhushan Bay, Meiliang Bay, and Gonghu Bay) where relatively heavy contamination has been reported, 19 and 21 from the southeastern area where less anthropogenic pollution was reported. Water samples were collected from the top 50 cm of the lake and sediment samples were collected from the top 30 cm of the lake bottom. Biota samples were collected from Meiliang Bay due to its its relatively high and homogeneous concentration of o-OPFRs. Water-to-plankton/fish bioaccumulation factors (BAFs) and sediment-to-invertebrate bioaccumulation factors (BSAFs) were calculated on the basis of biota concentrations and average water or sediment levels in Meiliang Bay.

  RDP was never detected in water samples and the detection frequency were 40 % for sediment samples with concentration ranging from <MDL (0.004 ng/g dw) to 1.2 ng/g dry weigth (dw). Regarding TPP, it was detected in 100% af water samples and 88 % of sediment samples, with concentration ranging from 0.094 to 3.7 ng/L and <MDL (0.036 ng/g dw) to 3.1 ng/g dw, respectively. Regarding bioaccumulation and trophic transfer of RDP, RDP was detected in 15 species with a detection frequency of 40%. The RDP concentration was 0.021 ng/g ww in plankton, <0.002−0.021 ng/g ww in invertebrates, and <0.002−0.22 ng/g ww in fish. BAF of RDP was much lower than those of monomeric organophosphorus FRs (m-PFRs) for equivalent logKow value. The estimated BSAFs of RDP was 14−26 g of TOC/g of lipid, similar to m-OPFRs with corresponding logKow values. The trophic transfer of RDP was not assessed due to its low detection frequency (40%).

- Matsukami et al., 2016, investigated the bioaccumulation of monomeric organophosphorus FRs (m-PFRs), and oligomeric organophosphorus FRs (o-PFRs) in 15 Nile tilapia (*Oreochromis niloticus*) fish muscle from an informal e-waste-processing area in Bui Dau, Hung Yen Province, northern Vietnam collected in December 2014. The body lengths, body weights, and lipid contents of the fishes (Nile tilapia (*Oreochromis niloticus*)) used for the method applications were 11-20 cm, 25-150 g, and 0.53-1.1%, respectively and samples were analysed by LC-ESI-MS. Detection frequency of RDP and TPP were 60% and 100%, respectively. The concentration ranged from <5 ng/g lipid weight (lw) (LOQ) to 8.2 ng/g lw (median = 6.1 ng/g) for

RDP and from 43 ng/g lw to 230 ng/g ng/g lw (median = 92 ng/g) for TPP. At this site, concentration of RDP median concentration in the upstream river sediment site was 2.3 ng/g dw and 23 ng/g dw in downstream river sediment sites. TPP median concentration was quite stable in upstream river site from 2012 to 2014 (<3 to 4.4 ng/g dw), increased at e-waste processing site from 7.3 to 200 ng/g dw and at downstream river sites from <3 to 36 ng/g dw (Matsukami et al., 2017). Considering that TPP have been detected with concentrations in the ng/g dw of sediment in this operating site (Matsukami et al., 2015), the results of this study suggest the potential bioaccumulation of TPP in fish muscle tissue. Nevertheless, the concentration of RDP in the tilapia muscle samples were one order of magnitude lower than those of TPP.

Summary and discussion of bioaccumulation

The available values for RDP log Kow indicate that RDP possess the potential to bioaccumulate. Despite variation in these value, estimation of BCF by EPIWeb v4.1 and performance of a read-across seem to indicate that RDP is not bioaccumulative even if bioacculmuation seem possible when no biotransformation occurs. There are only two environmental study providing data on the potential bioaccumulation and trophic transfer of RDP in the environment.

These data indicate that RDP can be found in the environment and in aquatic organisms with a low potential to bioaccumulate. On this basis, our English colleagues concluded that RDP does not appear to meet the B / vB criteria. Nevertheless, as no environmental data are available there is insufficient data to formally and definitively conclude on the B / vB. In conclusion, RDP seems to be not bioaccumulative and not very bioaccumulative according to the REACH PBT/vPvB criteria.

7.7.3.2. Terrestrial bioaccumulation

No relevant information available.

Regarding air-breathing organisms, the predicted Log Koa (octano-air partition coefficient) ranged from 9.91 to 13.32 depending on used log Kow (4.93; 5.5 and 7.41). Based on these log Kow and these estimated Log Koa, RDP fulfill the screening criteria for potential B in air-breathing organisms.

7.7.4. Secondary poisoning

Based on the available information, there is no indication of a bioaccumulation potential and, hence, secondary poisoning is not considered relevant.

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

Table 17

Method	Results	Remarks	Reference
Danio rerio (previous name: *Brachydanio rerio*) freshwater short-term toxicity to fish According to: EU Method C.1 (Acute Toxicity for Fish); OECD TG 203 (Fish, Acute Toxicity Test)	LC50 (96h): >100 mg/L WAF (nominal) based on: mortality NOEC (96h): >100 mg/L WAF (nominal) based on: mortality	1 (reliable without restriction) key study experimental study Test material (EC name): Fyrolflex RDP	Unpublished report, 2006b

Method	Results	Remarks	Reference
	NOEC (96h): >0.144 mg/L test mat. (meas. (initial)) based on: mortality		
Danio rerio (previous name: *Brachydanio rerio*) freshwater short-term toxicity to fish According to OECD TG 203 (Fish, Acute Toxicity Test) ; EU Method C.1 (Acute Toxicity for Fish)	LC50 (96h): 12.37 mg/L test mat. (nominal) based on: mortality (95%CL: 8.20 - 18.66 mg/l) LC50 (74h): 12.37 mg/L test mat. (nominal) based on: mortality (95%CL: 8.20 - 18.66 mg/l) LC50 (48h): 21.82 mg/L test mat. (nominal) based on: mortality (95%CL: 14.00 - 34.01 mg/l) NOEC (96h): 3.04 mg/L test mat. (nominal) based on: sublethal effects NOEC (96h): 6.69 mg/L test mat. (nominal) based on: mortality	2 (reliable with restriction) Supporting and experimental study Test material (EC name): Fyrolflex RDP	Unpublished report, 1996a

Two fish short-term study are available:

- All quality criteria were met, in the first one (Unpublished report, 2006b, K1) performed with *Danio rerio* according to OECD TG 203 using 10 and 100 mg/L WAF in OECD medium to determine the 96h-EC50 and NOEC for Fyrolflex RDP. The acute value was determined of being > WAF 100 mg/L which corresponds to a measured NOEC value of > 73 µg/L (measured value drop along the test in sample to value comprised between 73 to 144 µg/L depending on the tank). So the retained value for the NOEC value is the lowest in order to provide the highest security web.

- The second one (Unpublished report, 1996, K2) was performed with *Brachydanio rerio* (synonym name: *Danio rerio*) according to OECD TG 203. The fish were exposed to nominal concentration of 3.04, 6.08, 12.16, 24.32, 48.64 mg/L for 96h. A final 96h-EC50 value of 12.37 mg/L based on mortality well above the solubility range value was determined at the end of the experiment.

7.8.1.1.2. Long-term toxicity to fish

No data were available in the CSR.

7.8.1.2. Aquatic invertebrates

7.8.1.2.1. Short term toxicity to invertebrates

Table 18

Method	Results	Remarks	Reference
Daphnia magna freshwater flow-through according to OECD TG 202 (Daphnia sp. Acute Immobilisation Test)	EC50 - (48h): >14 µg/L (meas. (initial)) based on: mortality EC50 (48h): >20 µg/L test mat. (total fraction) (meas. (initial)) based on: mortality	1 (reliable without restriction) key study experimental study Test material Fyrolflex RDP	Unpublished report, 2019b
Daphnia magna freshwater flow-through according to EPA OPPTS 850.1010 (Aquatic Invertebrate Acute Toxicity Test, Freshwater	EC50 (48h): 0.76 mg/L test mat. (meas. (arithm. mean)) based on: mobility (95%CL: 0.63 - 0.90 mg/l)	2 (reliable with restrictions) supporting study experimental study	Unpublished report, 1999

Method	Results	Remarks	Reference
Daphnids) ; according to OECD TG 202 (Daphnia sp. Acute Immobilisation Test)	EC50 (24h): >3.2 mg/L test mat. (meas. (arithm. mean)) based on: mobility (Estimated by visual inspection)	Test material Fyrolflex RDP	
Daphnia magna freshwater static according to OECD TG 202 (Daphnia sp. Acute Immobilisation Test) ; according to EU Method C.2 (Acute Toxicity for Daphnia)	EC50 (48h): >100 mg/L test mat. - WAF (nominal) based on: mobility (average measured concentration for 100 mg/l WAF is 0.071 mg/l) NOEC (48h): 100 mg/L test mat. - WAF (nominal) based on: mobility (average measured concentration for 100 g/lWAF is 0.071 mg/l)	3 (not reliable) weight of evidence experimental study Test material Fyrolflex RDP	Unpublished report, 2006a

Three studies were available in the CSR.

- The key study was performed according the OECD TG 202 with *Daphnia magna* (Unpublished report, 2019b, K1). Briefly, *Daphnia magna* was exposed for 48h to nominal concentration of RDP of being 1.9, 3.8, 7.5, 15 and 30 µg/L corresponding to measured concentration of 0.94, 0.9, 2.5, 5.6 and 14 µg/L. All quality criteria were met at the exception of the RDP concentration which was not maintained ± 20% of the nominal concentration. The 48h-EC50 was determined of being > 20 µg/L for the Fyrolflex RDP (commercial solution, and 14 µg/L for the n=1 component). Despite this value is above the lowest solubility value, this EC50 value is in the rank of solubility provided in the CSR.

- The second study available (Unpublished report, 1999) was performed according the OECD 202. *Daphnia magna* was exposed for 48h to nominal concentration of RDP of being 0.65, 1.1, 1.8, 3.0, 5.0 mg/L corresponding to measured concentration of 0.43, 0.64, 1.5, 2.2 and 3.2 mg/L.The authors described a 48h-EC50 of 0.76 mg/L. Nevertheless, the value should have been lower. Indeed, at 0.43 mg/L, 5% immobilization were noted and at 0.64 mg/L, 60% of immobilization was observed. Based on this observation, the 48h-EC50 should be corrected for this supportive study.

- The last study was performed with *Daphnia magna* according to OECD TG 202 (Unpublished report, 2006a, K3). Briefly, *Daphnia magna* was exposed to 10 and 100 mg/L WAF in M4 medium for 48h. The average concentration for the 100 mg/L WAF was 69-74 µg/L and 18 µg/L for the 10 mg/L WAF. A 48h-EC50 > WAF 100 mg/L and a NOEC of WAF 100mg/L were determined.

Another data was available in literature: Waajiers et al., 2013 assessed the aquatic toxicity of RDP (polymer consisting of mostly n = 1–3, CAS RN. 57583-54-7, 82%, ICL) against *Daphnia magna* according to the OECD TG 202. First, they assessed the effect of saturated water solutions (ISO medium without additional buffer, pH = 7.5 ± 0.5, T = 20 °C ± 1, here defined as Sw) on the daphnids. An excess of compound was stirred for 7 days in ISO medium, filtered and tested for toxicity with a control. Exceptions was for TPP which was spiked with methanol (0.08%) at the highest value reported in literature for Sw (2 mg/L nominal), a solvent control was also realised. Second, D. *magna* were exposed (4 replicates) for 48 h in immobility tests, randomly distributed, exposed at 20 ± 1 °C, with a light-dark regime of 16:8 h. The experiment was started by introducing 5 neonates (younger than 24 h) and the immobility was scored at 24 and 48 h. Homogeneity of the samples was checked. The toxicity of RDP could not be properly evaluated as it formed an

emulsion in the test solution. The solutions obtained in this study after one week of stirring (emulsion; 66 ± 61 mg/L) exerted no adverse effect on the daphnids.

The measured experimental concentrations were 152.58 (±16.65), 44.85 (±6.09) and 22.34 (±4.89) (n=3).

7.8.1.2.2. Long-term toxicity to invertebrates

Table 19

Method	Results	Remarks	Reference
Daphnia magna freshwater Long term toxicity according to OECD TG 211 (*Daphnia* sp. Reproduction Test); according to EPA OPPTS 850.1300 (Daphnid Chronic Toxicity Test)	NOEC (21d): 21 µg/L test mat. (meas. (initial)) based on: mortality NOEC (21d): 21 µg/L test mat. (meas. (initial)) based on: reproduction NOEC (21d): 21 µg/L test mat. (meas. (initial)) based on: growth	1 (reliable without restriction) key study experimental study Test material Fyrolflex RDP	Unpublished report, 2014
Daphnia magna freshwater Long term toxicity according to OECD TG 211 (*Daphnia* sp. Reproduction Test)	NOEC (21d): 0.021 mg/L test mat. (meas. (TWA)) based on: reproduction NOEC (21d): 0.064 mg/L test mat. (nominal) based on: reproduction LOEC (21d): 0.065 mg/L test mat. (meas. (TWA)) based on: reproduction LOEC (21d): 0.2 mg/L test mat. (nominal) based on: reproduction EC50 (21d): 0.037 mg/L test mat. (meas. (TWA)) based on: immobilisation (95%CL: 0.021 - 0.065 mg/l) EC50 (21d): 0.11 mg/L test mat. (nominal) based on: reproduction (95%CL: 0.064 - 0.20 mg/l) EC50 (21d): >0.021 - <0.065 mg/L test mat. (meas. (TWA)) based on: reproduction	1 (reliable without restriction) key study experimental study Test material Fyrolflex RDP	Unpublished report, 2001

Two long-term studies with invertebrates were available.

- The study performed by Unpublished report, 2001, was considered of not being K1 anymore because the test substance was used at a concentration above the solubility value. Nevertheless, the same way to proceed was used in the assay with *Danio rerio* and the study was not downgraded. Beside this, the study quality is considered good and the K1 score seems justified. At a concentration >0.20 mg/L, a white heterogeneous dispersion was observed in the assay. The measured 21d-EC50 based on reproduction was 0.037 mg/L and the NOEC value was 0.021 mg/L.

- Based on the uncertainties of the quality score of the previous data, a second study on Daphnia magna reproduction was performed under flow-through according to OECD TG 211 with Fyrolflex RDP (Unpublished report, 2014). The measured 21-day NOEC based

on reproduction was 0.021 mg/L, similar to what was observed previously. Despite the good quality of the study some limitation were noted. The food used for the daphnids exceed the value recommended by OECD (0.71 mgC/ daphnia/ day > 0.1mgC/ daphnia/ day). It was justified as being necessary to maintain sufficient feeding for reproduction rate in the flow-through experiment. It cannot be excluded that some adsorption of the test material had occurred due to this food excess. Another anomaly was observed, corresponding to the presence of TPP in several subsamples of the negative control (4/5) and solvent control (1/5). Despite their low amount, comprised between 0.224 to 1.30 µg/L, the detection value is > LOQ (0.150 µg/L).

7.8.1.3. Algae and aquatic plants

Three studies with algae were available.

- The first study available was performed according to OECD TG 201 (Unpublished report, 2006, K3). Briefly, *Raphidocelis subcapitata* was exposed to 10 and 100 mg/L WAF in OECD medium for 72h. The average concentration for the 100 mg/L WAF was 40 µg/L and 9 µg/L for the 10 mg/L WAF, corresponding to the LOEC and NOEC value, respectively. The quality criteria were met, and a small variation was observed on the use of at 150 mg/L NaHCO3 concentration instead a recommended value of 50 mg/L, allowing a better control of the pH variation.

- The second available study was performed according to OECD TG 201 (Unpublished report, 1995, K2). Briefly, *Raphidocelis subcapitata* was exposed to nominal concentration of RDP of being 0, 3.04, 6.08, 12.16, 24.32 and 48.64 mg/L in the presence of an emulsifier, tween 80, a positive control, potassium dichromate for 72h. All quality criteria were met. The LOEC was determined of being 48.64 mg/L and the NOEC of being 24.32 mg/L. At the end of exposure, the maximum recovery were comprised between 76-88%.

- The third study was performed according to OECD TG 201 (Unpublished report, 2019a, K1). Briefly, *Raphidocelis subcapitata Pseudokirchneriella subcapitata* was exposed for 72h to nominal concentration of RDP of being 1.9, 3.8, 7.5, 15 and 30 µg/L corresponding to measured concentration of 0.83, 1.8, 3.5, 6.7 and 13 µg/L (for the n=1 component). All quality criteria were met, no floculation, aggregation, adherence to test chamber was observed. The 72h-EC50 was determined of being > 13 µg/L and the NOEC value was 13 µg/L (measured value). As there was some decay in test substance concentration in the different sample, the measured value for the NOEC should be used in the risk assessment and PEC/PNEC determination to better reflect this phenomenon, always observed in all experimentation.

7.8.1.4. Sediment organisms

No relevant information available

7.8.1.5. Other aquatic organisms

No relevant information available

7.8.2. Terrestrial compartment

No relevant information available

7.8.3. Microbiological activity in sewage treatment systems

In the CSR, a study on the effects of RDP on *Pseudomonas putida* was available (Unpublished report, 1995b, K1). The study was performed according to DIN 38412-8 and provide a 2 min EC-50 > 12.16 mg/L based on the inhibition of total respiration.

In the literature, Liang et al. 2018, investigated the occurrence and distribution of oligomeric organophosphorus flame retardants in different treatment stages of a sewage treatment plant processesing approximately 400 000 m3/day of wastewater serving about 814 000 inhabitants of Beijing, China. The STP employs anaerobic/anoxic/aerobic (A/A/O) tanks in combination with advanced oxidation processes (AOPs). A sampling campaign was carried out on July 1, 2014, a normal dry-weather condition day and samples were collected at the outlet of each treatment stage, and were obtained by combining four (every 6 h) grab samples over a period of 24 h. Analyses were performed with LC-MS/MS and UPLC-MS/ MS. RDP was detected in the solid phase of samples obtained from different treatment stages of the STP in the range of 0.44-3.45 ng/g dw, the concentration level in the aqueous phase of these samples were all below the corresponding MDLs (0.40 ng/L). RDP was ubiquitous in the suspended solids of sewage and sludge samples, which can be explained by their strong solid or sludge sorption tendency with high octanol-water partition coefficient (RDP, log Kow= 7.41). RDP concentrations in suspended solids of aerobic (3.45 ng/g dw) and return sludge (2.90 ng/g dw) samples were larger than those of other samples (0.44-0.79 ng/g dw).

RDP was mainly degraded by activated sludge in the secondary treatment, with a mass loss fraction of 83.3%. This shows that both traditional processes and AOPs can contribute to the removal of RDP.

7.8.4. PNEC derivation and other hazard conclusions

Table 20

PNEC DERIVATION AND OTHER HAZARD CONCLUSIONS		
Hazard assessment conclusion for the environment compartment	**Hazard conclusion**	**Remarks/Justification**
Freshwater	PNEC aqua (freshwater): 0.42µg/L	Assessment factor: 50 (two chronic aquatic toxicity tests representing two trophic levels (algae, invertebrates). Extrapolation method: assessment factor OECD TG 211 (Daphnia reproduction study; NOEC of 21 µg/L, mean measured)
Marine water	PNEC aqua (marine water): 0.042µg/L	Assessment factor: 500 (two chronic aquatic toxicity tests representing two trophic levels (algae, invertebrates). Extrapolation method: assessment factor OECD TG 211 (Daphnia reproduction study; NOEC of 21 µg/L, mean measured)
Sediments (freshwater)	PNEC sediment (freshwater): 0.015mg/kg sediment dw	Extrapolation method: equilibrium partitioning method PNEC sediment (freshwater) As no toxicity data for sediment organisms is available, the PNECsediement (freshwater) is calculated using the Equilibrium Partitioning Method as described in guidance document R10. Based on a PNECaqua (freshwater) of 0.18 ug/l and a log Kow of 4.93 (used to calculate a log Koc of 4.09 in EUSES 2.1) the PNECsediment (freshwater) is 0.52 mg/kg sediment dw
Sediments (marine water)	PNEC sediment (marine water): 0.002mg/kg	Extrapolation method: equilibrium partitioning method

	sediment dw	PNEC sediment (marine water) As no toxicity data for sediment organisms is available, the PNECsediement (marine water) is calculated using the Equilibrium Partitioning Method as described in guidance document R10. Based on a PNECaqua (marine water) of 0.018 ug/l and a log Kow of 4.93 (used to calculate a log Koc of 4.09 in EUSES 2.1) the PNECsediment (marine water) is 0.05 mg/kg sediment dw.
Sewage treatment plant	PNEC STP: 12.16 mg/L	Assessment factor: 10 Extrapolation method: assessment factor PNEC STP An activated sludge respiration inhibition test is available. The result is that no significant effects were observed at the highest concentration tested (121.6 mg/l). Taking into account the assessment factor of 10 (Table R.10.6 in guidance document R.10, "Dose (concentration)-response regarding environment") the PNEC STP is >12.16 mg/l
Soil	PNEC soil: 0.154 mg/$kg_{soil\ dw}$	Extrapolation method: equilibrium partitioning method PNEC soil As no toxicity data for soil organisms is available, the PNECsoil is calculated using the Equilibrium Partitioning Method as described in guidance document R10. Based on a PNECaqua (freshwater) of 0.42 ug/l and a log Kow of 4.93 (used to calculate a log Koc of 4.09 in EUSES 2.1) the PNECsoil is 0.154 mg/kg soil dw
Air	No hazard identified	-
Secondary poisoning	PNEC oral: 2.53mg/kg	Assessment factor: 300 A 28d-NOAEL of 38 mg/kg bodyweight in rats (older than 6 weeks) is available. This NOAEL is converted to a NOECoral of 0.00076 kg/kg food using a conversion factor of 20. This NOECoral is converted to a PNECoral by dividing it by an assessment factor of 300. This results in a PNECoral of 8.44 mg/kg food

7.8.5. Conclusions for classification and labelling

Based on the results of acute studies it seems that there are acute effects at the water solubility limit of the substance, because the measured EC50 values in invertebrates are below the value of 1 mg/L. Therefore, the substance can be classified for acute hazards as Aquatic Acute 1 with a M-factor of 10 (EC50 in *Daphnia magna* comprised between 0.01 and 0.1 mg/L).

Reliable chronic data is available for two trophic levels (algae, invertebrates). The lowest reported NOEC is 0.021 mg/L for *Daphnia magna* (reproduction). Based on this information, the substance can be classified for long-term hazards as Aquatic Chronic 2.

7.9. Human Health hazard assessment

Only endpoints relevant in the assessment of the concerns, i.e. the endocrine disruption potential, neurotoxicity and immunotoxicity were assessed in details. Toxicokinetics is also presented.

7.9.1. Toxicokinetics

Skin absorption was tested (Unpublished report, 1994) *in vivo* in male Sprague-Dawley rats in a non-guideline study rated with Klimisch score 2 in the registration dossier. RDP (no information on purity) was non-occlusively applied at a dose of 100 mg/kg in polyethylene glycol-400 (PEG-400) or neat. A single animal was used at each experimental condition. Dermal absorption was higher (approx. x4) when RDP was applied neat compared to application in PEG-400. Thirty-six hours after the end of exposure to neat RDP, approximately 15% of radioactivity have been absorbed (8.72% in the carcass, 1.47% in urine, 4.42% in feces).

Metabolism and toxicokinetic of RDP (purity >99%) were examined *in vivo* in mice, rats and primates by different routes of exposure (Freundenthal et al., 2000).

Table 21 – Test conditions and excretion routes in Freudenthal et al. 2000

Species	Route	Dose	Samples collected	Excretion routes
Mouse (B6C3F1), n=8	Intravenous	100 mg/kg (single dose)	Exhaled air collected. Urine and feces collected at 2, 6, 12 and 24 h and 2, 3, 4, 5, 6 and 7 days after dosing Plasma sample NOT collected	No data (only metabolism determined)
Rat (Sprague-Dawley), n=5	Intravenous	100 mg/kg (single dose)	Exhaled air collected. Urine and feces collected at 2, 6, 12 and 24 h and 2, 3, 4, 5, 6, 7, 8, 10 and 14 days after dosing Plasma sample at interim time points	At day 7: 13% of dose excreted in urine, 45% in feces, 7% in exhaled air. No sex differences.
Rat (Sprague-Dawley), n=2/sex	Intravenous	100 mg/kg (single dose)	Exhaled air, urine and feces collected for 14 days. Collection of tissue samples at the end of the collection period to determine distribution	At day 14, total body burden < 4% of the administered dose: no preferential sites of RDP or metabolite deposition other than the lung.
Primate (cynomolgus), n=3	Intravenous	100 mg/kg (single dose)	Exhaled air NOT collected. Urine and feces collected at 2, 6, 12 and 24 h and 2, 3, 4, 5, 6, 7, 8, 9, 10, 14, 21 and 28 days after dosing Plasma sample at interim time points	At day 7: 24% of dose excreted in urine, 26% in feces (exhaled air not determined).
Rat (SD), n=4	Inhalation (nose-only)	Target: 100 mg/kg Inhalation for 6h of aerosol with average particle size of 3 µm	Exhaled air collected. Urine and feces collected at 2, 6, 12 and 24 h and 2, 3, 4, 5, 6, 7, 8, 9, 10, 14, 21 and 28 days after dosing Plasma sample at interim time points	10 and 7% of dose excreted in urine in males and females; 60 and 52% in feces in males and females (exhaled air not determined).

Rat (SD), n=5	Dermal	Target: 100 mg/kg (applied non occlusively on shaved skin, approx 20% of body surface, for 6 h)	Exhaled air collected. Urine and feces collected at 12 and 24 h and 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 21 and 28 days after dosing Plasma sample at interim time points	At day 7: 7% of dose excreted in urine, 32% in feces, 1% in exhaled air. Higher AUC and half-life in females
Primate (cynomolgus), n=3	Dermal	Target: 100 mg/kg (applied non occlusively on shaved skin, approx 20% of body surface, for 6 h)	Exhaled air NOT collected. Urine and feces collected at 2, 6, 12 and 24 h and 2, 3, 4, 5, 6, 7, 8, 9, 10, 14, 21 and 28 days after dosing Plasma sample at interim time points	At day 7: 1% of dose excreted in urine, 1% in feces (exhaled air not determined). At day 28: 4% of dose excreted in urine and 5% in feces
Rat (SD), n=6	Oral	100 mg/kg (single dose by gavage)	Exhaled air collected. Urine and feces collected at 2, 6, 12 and 24 h and 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 21 and 28 days after dosing Plasma sample at interim time points	At day 1: 7% of dose excreted in urine, 80% in feces (including unabsorbed RDP). At day 7: ; all radioactivity excreted; 5% in exhaled air

Toxicokinetic parameters (Table 22 below and excretion data in Table 21 above)

The influence of the route of exposure on pharmacokinetic was investigated in the rat. Then, comparative pharmacokinetics were performed in the rat, mouse and monkey by intravenous (iv) route.

Excretion in feces is the predominant route of excretion in rats: it is 3-6 times higher than urinary excretion by iv, dermal and inhalation routes and 11.4 times higher by oral route probably due to a contribution of unabsorbed RDP. In contrast, excretion is as important in urine as in feces in primates (iv and dermal routes). Urinary excretion is therefore more predominant in primates than in rats (24% vs 13% of the dose at day 7 after iv administration). The expired air was a minor route of excretion.

Distribution in rats after inhalation and iv administration show that lung may serve as a short-term storage for RDP. Autoradiography showed the radioactivity to reside in the pulmonary vasculature. It was not observed after oral or dermal administration. By iv, the body burden of radioactivity was approximately 10% after 7 days (6.8% in the lungs and 3.2% in other tissues and in the carcass) and less than 4% after 14 days (2% in the lungs and 1.9% in other tissues and in the carcass). Other than the lungs, no preferential sites of RDP or metabolite deposition were identied but fat and liver contained slightly more radioactivity on a unit weight basis than kidneys, testes/ovaries, brain, kidneys, skin, spleen or the residual carcass (3.6 times higher concentration in fat than in residual carcass at day 14).

Half-life in primates was longer (5.15 ± 1.11 days) than that observed in rats (2.38 ± 0.39 days) by iv and the maximal concentration (Cmax) was higher so that the area under the curve (AUC) was considerably higher in primates compared to rats. Cmax was influenced by the route of exposure and was higher after inhalation than after oral or dermal route (12.13 µg/ml vs 3.03 and 0.43, respectively).

These differences may result in differences in the systemic exposure to urinary metabolites, e.g. resorcinol, between rats and primates:

- By oral route (gavage) in the rat 80% of the administered dose was excreted in feces on day 1. A fraction reflect excretion of unabsorbed RDP and oral absorption may have

been overestimated. Bioavailability was calculated by comparison of the AUC of oral vs iv routes adjusted for respective doses and was 61%. Bioavailability after dermal absorption in rats was calculated to be 21% of the dose, which is consistent with absorption results reported in the previous study (Unpublished report, 1994).

- In primates, dermal absorption was approximately 9% but this result may represent an underestimation as a low rate of radioactivity recovery (approx. 70%) was reported in this part of the study. Exhaled air was not collected during this part of the study. Bioavailability by inhalation could not be determined due to technical limitations but systemic exposure as measured by AUC was similar to AUC by iv and higher than AUC measured by oral route.

Sex differences were not observed in rats except by dermal route, with higher AUC and half-life in females than in males.

Table 22 - Toxicokinetic parameters (mean ± standard deviation)

Parameter (unit)	Cmax (µg equiv/ml)	Tmax (h)	AUC (µg equiv x h/ml)	t1/2 (day)	Systemic bio-availability
Primate (iv)	81.86 ± 22.08	0.08 ± 0.00	1895.0 ± 213	5.15 ± 1.11	100%
Rat (iv)	29.20 ± 16.43	0.10 ± 0.06	453.0 ± 119.0	2.38 ± 0.39	100%
Rat (dermal)	0.43 ± 0.15	2.30 ± 1.25	68.0 ± 28.0	3.67 ± 0.41	20%
Rat (inhal.)	12.13 ± 8.11	13.16 ± 17.74	273.0 ± 242	2.51 ± 0.95	ND but >oral
Rat (oral)	3.03 ± 0.67	0.88 ± 0.84	263.0 ± 108	2.73 ± 0.28	61%

ND : not determined; t1/2: half-life, Tmax: time of maximal concentration

Metabolism

A metabolite profile was obtained for several urine and feces samples from each test animal. Individual metabolites that accounted for at least 5% of the administered dose were isolated and identified. Due to radiolabeling of the resorcinol ring, formation of diphenyl phosphate and its metabolites cannot be detected under this protocol. The same four major metabolites are formed by all three species in feces (see Figure 2). The relative amount of the four metabolites in rats after oral administration are RDP half-ester (or hydroxyl-TPP) ≈ 30% of the administered dose, dihydroxy-RDP ≈ 10–15%, and hydroxy-RDP half-ester and hydroxy-RDP ≈ 5–10% each. Very little unmetabolised RDP is detected in the urine and feces of animals exposed by iv, inhalation or dermal routes. It is detected only following oral administration in feces and it may correspond to unabsorbed RDP. However no detailed quantitative information is provided.

The influence of the route of exposure in the quantitative metabolite profile is not discussed neither in the publication nor in the study reports available to the eMSCA (Unpublished report 1997a and Unpublished report 1997b).

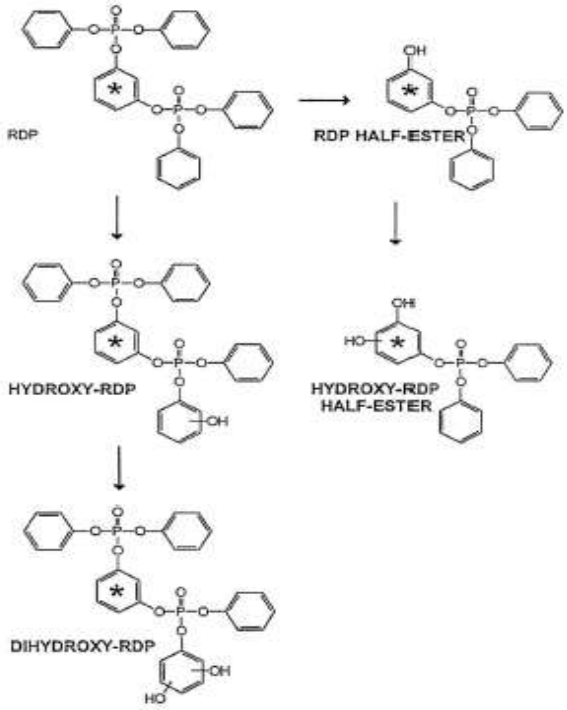


Figure 2 – Four major metabolites identified from the feces of rats, mice and monkeys

Urinary metabolites from mouse, monkey and rat were found very similar (detailed data not shown). The three major metabolites are resorcinyl glucuronide, resorcinyl sulfate and resorcinol (amounts not provided). Hydroxylated TPP is not reported as a predominant metabolite although hydroxylated TPP is the proposed first step to formation of resorcinol and resorcinol conjugates. A scheme for the formation of the urinary metabolite is shown in Figure 3.

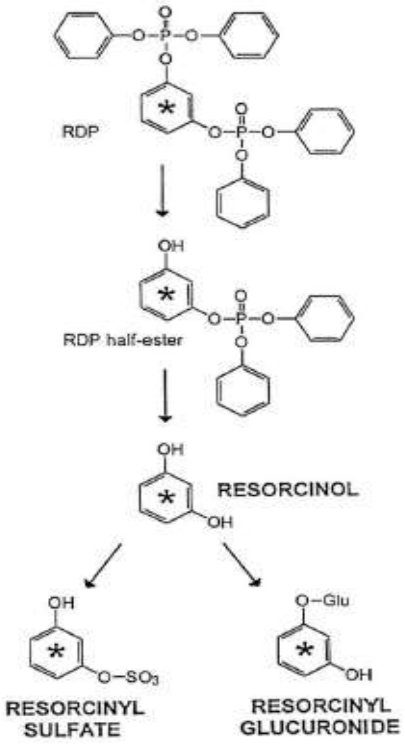


Figure 3 – Metabolic pathway to the three major metabolites found in the urine of rats, mice and monkeys

In a recent *in vitro* study from Ballesteros-Gómez et al. (2015), the metabolites of RDP (98% purity) and its oligomers were investigated by liquid chromatography coupled with quadrupole-high-resolution mass spectrometry after incubation for 2 hours with human liver microsomes (n=50, mixed gender) or human liver cytosol. Mono- and dihydroxy-metabolites were detected. RDP and its oligomers were readily hydrolysed, giving rise to diphenyl phosphate (DPHP) and a variety of mono- and di-hydroxylated compounds. Di-hydroxy-TPP, di-hydroxy-RDP, para-hydroxy-TPP and para-hydroxy RDP were the most abundant ones. No resorcinol or resorcinol conjugates were detected. Regarding RDP oligomers, only a hydroxymetabolite of the dimer could be detected. The glucuronidated and sulfated conjugates of the metabolites were detected when RDP was incubated with microsomes in the presence of uridine 5′-diphosphoglucuronic acid or with cytosols in the presence of adenosine 3′-phosphate 5′-phosphosulfate, respectively.

In this study, the hydrolysis of RDP was also tested in buffer at 37°C for 30 min to simulate physiological conditions. DPHP, meta-hydroxy-TPP and RDP with loss of a phenol group were formed from RDP and meta-hydroxylated hydrolysis products of RDP oligomers.

Quantitative comparison however suggested that DPHP and hydroxyl metabolites formed in the first part of the study are not only hydrolysis products of RDP but also metabolites. It was also suggested that para-hydroxy metabolites were produced by CYP enzymes while meta-hydroxy metabolites were not and could be present in the human body due to hydrolysis of RDP.

Metabolism of TPP was also tested. DPHP was formed from TPP as well as hydroxylated-TPP. It was concluded that DPHP, that is reported in biomonitoring studies and generally associated to exposure to TPP, can also be formed from RDP. It is a common metabolite to TPP and RDP.

This was further confirmed in another study (Van den Eede et al., 2016) showing that when TPP is incubated with primary human hepatocytes, the major metabolites formed were diphenylphosphate, mono, and di-hydroxylated TPP. No trace of free resorcinol was detected *in vitro*.

In a recent human biomonitoring study (Hou et al., 2020), RDP was detected by high-performance liquid chromatography in respectively 18% (range: <0.27-5.36 ng/ml), 0% and 10% (range: <0.054–0.078 ng/ml) of the samples from 52 paired whole blood, serum and urine samples collected in Beijing (China). This confirms that RDP is absorbed and can be excreted in urine (unmetabolised RDP). A lower detection frequency and lower detection levels in urine compared to whole blood support that RDP is metabolised to an important extent. DPHP was detected in all whole blood and urine samples and in 61% of serum samples. DPHP can be formed from RDP but also from multiple other organophosphate flame retardants that were detected in the study including TPP.

Conclusion

The available data show that RDP is well absorbed by inhalation and oral route (approx. 80%) and to a lesser extent by dermal route (20%) in the rat. Similar metabolites are formed in rats, mice and cynomolgus monkeys and consist mainly in hydroxylated and dihydroxylated forms of RDP and of TPP in the feces and in resorcinol and its conjugates in urine. Very little unmetabolised RDP is detected in the urine of experimental animals but it has been detected in human urine samples. The predominant route of excretion in experimental animals is the fecal route and the urinary route to a lesser extent.

A higher bioavailability is observed in primates compared to rats and the urinary route of excretion is of higher importance in primates than in rats. Effects related to the urinary metabolite resorcinol may therefore be underestimated in studies performed in rats.

7.9.2. Acute toxicity and Corrosion/Irritation

Not evaluated during SEv.

7.9.3. Sensitisation

Not evaluated during SEv.

7.9.4. Repeated dose toxicity

In a 28-day study performed according to OECD TG 412 (Henrich et al., 2000a, Unpublished report, 1994a), Sprague-Dawley rats (n=10/sex/group) were exposed by inhalation (nose only) to an aerosol of Fyroflex RDP (purity: 65-80% RDP (n=1), 15-30% higher oligomers, <5% TPP; MMAD: 1.39-1.70 µM) at concentrations of 0, 0.1, 0.5 and 2.0 mg/l 6h/d, 5d/wk for four weeks. A satellite group of control and high-dose animals were held for an additional 60-day recovery period after the end of the exposure.

No death and no clinical signs were reported. Body weight was significantly decreased in high dose males from week 1. The decrease was statistically significant during the exposure period except at the 4th week and during the 5 first weeks of the recovery period. At the end of the exposure period, mean body weight gain of high dose males was decreased by approximately 20%. Food consumption was also decreased in this group of animals. No effect was observed in female body weight during exposure. In the recovery period, the body weight of high-dose females was higher than control with statistical significance observed only at week 5 post-exposure (+9%). The significance of this observation is unknown.

The following biochemical parameters were statistically significantly modified: decreased glucose in high-dose males and females; increased globulin in mid-dose females; decreased total bilirubin in mid- and high-dose males; increased erythrocyte count, hemoglobin and haematocrit in low-dose females.

The activity of plasma cholinesterase was significantly decreased at the end of exposure in high-dose males (15% decrease) and in mid-dose and high-dose females (38 and 64% of decrease). The decrease (15%) was still significantly present after 60 days of recovery in high-dose females (not investigated in mid-dose females). No effect was observed on erythrocyte cholinesterase. Monocyte nonspecific esterase (MNSE) activity levels were increased in low- and mid-dose rats (sexes combined, +44% and +76%, respectively) at the end of the 28-day exposure period (statistical significance not specified).

The effect on organ weight were noted in the liver and in the lung. A dose-related increase in absolute and relative lung weights was seen, with statistically significant increases in mid- and high-dose animals after 28 days of exposure. The increases in lung weights persisted in the high-dose recovery animals at the end of the 60-day recovery period. In addition, mean absolute liver weights were significantly increased in high-dose females, and mean relative liver weights were significantly increased in mid- and high-dose females and high-dose males after 28 days of exposure. No effect was observed on adrenals or thyroid weights.

Macroscopic and microscopic findings were mainly restricted to the lung. The lesions consist in alveolar histiocytosis in all mid- and high-dose animals at the end of exposure. Large macrophages infiltrated the perivascular adventitia and alveolar septae, and lined and filled the lumen of alveoli located near terminal bronchioles. Occasionally, terminal bronchioles contained focal areas of minimal epithelial hyperplasia. These lesions progressed into chronic foreign body inflammation at the end of the 60-day recovery period in high-dose animals (no recovery group at mid-dose). Macrophages had formed well-defined foci in the lung, and a greater lymphocyte infiltration was present and had migrated to intrapulmonary lymphoid tissue. This was considered by the author as a typical response to a noncytotoxic, water-insoluble foreign material that has reached the alveolar zone of the lung. It confirms that RDP is not easily eliminated from the lung and is consistent with observation of some RDP storage in the lung in the toxicokinetic experiment performed by inhalation. The adrenals and the thyroid were histotologically examined in the control and high-dose animals and no findings were noted. In addition, lymph node hyperplasia was

noted at the end of exposure in one animal of each sex at the highest concentration. Cardiomyopathy was also noted in 3/20 animals exposed to the highest concentration.

An oral 90-day study was conducted by gavage (Unpublished report 2019c) in accordance to OECD TG 408. Fyrolflex RDP (purity considered to be 100%, certificate of analysis stating TPP<5%) in corn oil was administered at doses of 0, 30, 100, 300, 1000 mg/kg to Sprague-Dawley rats. Two control satellite groups (n=10/sex/group) and one satellite group for each test dose were conducted in addition to main groups (n=10/sex/group).

No death and no clinical signs were reported. Body weight gain was significantly decreased in high dose males whereas food consumption was not decreased. Sporadic changes in hematology and blood chemistry were noted without clear relation to treatment. The most noticeable change was a decrease in mean cell haemoglobin concentration in males from 300 mg/kg/d and in females from 30 mg/kg/d and low alkaline phosphatase in males from 100 mg/kg/d and in females from 30 mg/kg/d.

Measures of the various cholinesterase (ChE) activities were performed at week 12. Plasma ChE was significantly and dose-dependently decreased in both males and females from the lowest test dose. Erythrocyte ChE was significantly decreased in high dose females. A non-significant decrease is also reported in males. No effect was observed on brain ChE activity. No significant effect was observed on sensory reactivity, grip strength and motor activity measured at week 12 in both main and satellite groups (males and females analysed separately). Motor activity war measured with the Rodent Activity Monitoring System by counting infra-red beam breaks over ten 6-minute intervals (one hour total). Ten beams were set at two height levels (five low and five high) to detect cage floor and rearing activity respectively.

A dose-related increase in relative liver weight was observed in males and females from the lowest dose. Minimal to slight hypertrophy was observed from 100 mg/kg/d. Increase in adrenals relative weight was observed at all doses in females (103.5%, 115.8% ($p<0.05$), 117.5% ($p<0.05$) and 119.3% ($p<0.05$) of controls), without any histological findings (10/20 animals/sex analysed in the control and high-dose group only). Thyroid weight was not measured but minimal to slight follicular cell hypertrophy was observed from 100 mg/kg in males and females with a dose-related incidence and/or severity. Thyroid hormones were not measured (study performed from February to November 2018 while mandatory only in the update of the OECD TG 408 adopted in June 2018)

Two additional studies were performed by intraperitoneal route (ip) in SD rats.

- In a 28-day study (Unpublished report 1989b), SD rats (n=12/sex/group) were exposed to 0, 0.000175, 0.00175, 0.5, 50, 500 mg/kg/d RDP (purity not known). An additional comparative control group was exposed to 50 mg/kg/d of TPP. No death, no clinical signs, no effect on BW were reported. Plasma ChE activity were decreased at 50 (females) and 500 (males and females) mg/kg/d (effect also detected in females with TPP). No effect was observed on erythrocyte ChE activity. Hepatic and peritoneal monocytic non-specific esterase activity was decreased from 50 mg/kg/d. Relative liver weight was increased at at 500 mg/kg/d. Granulomatous inflammatory response was observed in the mesentery and in adipose tissue of some visceral organs (all doses). Thyroid of all rats in the control group, in test groups exposed from 50 mg/kg/d and in the TPP group had the histological appearance of slight to moderate activity (histopathology not performed at lower doses). Thyroid weight was not measured.

- The induction of multinucleated giant cells in mesentery nodes and their recovery was investigated (Unpublished report 1990). This effect was present after 14 days of IP injection of 500 mg/kg/d RDP (purity not known). It was accompanied by minimal to moderate mesenteric fat necrosis and mesenteric granulomatous inflammation that increased in severity from day 6 or 12 to 26 or 29 and decreased from day 29 or 36 to week 28 (not fully reversed), respectively. No death, no clinical signs and no effect on body weight were observed. Plasma ChE was decreased for the first 8 weeks and progressively returned to normal thereafter (week 20) while no effect was observed on

erythrocyte ChE activity. The report notes that the thyroid of all rats had the histological appearance of moderate activity at day 14 and week 28 but was not considered as related to treatment. Thyroid weight not measured. No control group was included in this study.

Conclusion

The lung and liver were affected by inhalation in a 28-day study whereas liver, adrenals and thyroid were affected in a 90-day study by gavage. In all studies, plasma ChE activities were consistently decreased with indications of a long-term effect (not reversible after 60 days further to a 28-day exposure by inhalation, decrease for several weeks in the IP recovery study). This may also result from continuous exposure due to storage at the site of contact. Erythrocyte ChE activity was decreased only in females exposed to 1000 mg/kg/d by gavage. Brain ChE was not affected in the only study repeated-dose toxicity study in which it was measured (90-day gavage study) and sensory reactivity, grip strength and motor activity were unaffected.

7.9.5. Mutagenicity

Not evaluated during SEv.

7.9.6. Carcinogenicity

No carcinogenicity data available.

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

7.9.7.1. Multi-generation study

A two-generation study (Henrich et al., 2000b) was performed in Sprague-Dawley rats with a protocol equivalent to an OECD TG 416. Fyrolflex RDP (purity not specified) was administered in diet at concentrations of 0, 1000, 10 000 or 20 000 ppm (approximately equivalent to 0, 55, 600 and 1200 mg/kg bw in adults). Concentrations were confirmed analytically on a regular basis and stability confirmed over two weeks (diet prepared once a week). The parental generation (n=30/sex/group) was fed the appropriate diet for 10 weeks prior to mating, during a 2-week mating period, through gestation, lactation, and until sacrifice. Selected F1 animals were fed the same diet for 11 weeks prior to mating, during mating, gestation, lactation, weaning, and until sacrifice. F2 generation was not intentionally exposed to the test diet and was sacrificed after weaning. Thyroid were neither examined nor weighted in this study.

In the parental generation (P1), a decreased body weight was observed in mid- and high dose males after the first week and was persistent throughout the study (up to -5 and -10% approx.). Transient decreases in food consumption were also observed in high-dose males.

Increase in absolute and relative adrenal glands weight were noted in males at mid- and high-doses (+22% relative weight at both doses) and females at all doses (+14, 24 and 24% relative weight, respectively). Adrenals were not examined histologically.
Increase in liver weight was noted in males from the mid- dose and in females at all doses (absolute and relative; dose-related). Periportal hypertrophy was observed at high dose (not investigated at lower doses).

An increase in the relative weight of testis and epididymis at high dose and of cauda epididymis from mid-dose was observed. No findings were reported at histopathological examination.

In F1 animals, pup bodyweight was not affected at birth but was decreased in mid- and high-dose groups from postnatal day (PND) 7, reaching respectively -19 and -28% at

PND21. Food consumption was also significantly decreased at PND21 in mid- (-12%) and high-dose (-17%) dams, reflecting cumulative maternal and pup consumption. Post-weaning, the food consumption and body weight gain were not affected but a significant difference in body weight across groups persisted until adulthood at mid- and high-doses as well as at low dose (-9%, -11% and -13% respectively at week 16 in males). Vaginal opening and preputial separation were delayed of 3 to 5 days in the 500 and 1000 mg/kg/day bw groups. Anogenital distance was not modified. Nipple retention not measured. In F1 adults, effects similar to P1 generation were observed on adrenals, liver and male reproductive organs: relative adrenal weight was increased from low dose in males and mid- dose in females. Relative liver weight was increased from mid-dose in males and low-dose males in females. Periportal hypertrophy was observed at high dose.

An increase in relative weight of testis and epididymis was observed from mid-dose and of cauda epididymis at high-dose. No findings were reported at histopathological examination. In addition, an increase in the relative brain weight in males (all doses) and females (significant at low and high doses) was observed. Brain was not examined histologically.
In F2 pups, similarly to F1, no effect on bodyweight was observed at birth but body weights of low-, mid- and high-dose pups were significantly decreased compared to control pups from PND 4 and up to the termination of the study at PND21, reaching respectively -7%, -23 and -28% at PND21. Cumulative maternal and pup food consumption at PND21 was respectively -2, -4 and -7%, reaching significance only at the highest dose.

According to the authors (Henrich et al., 2000b), the delay of postnatal weight growth was attributed to food aversion. Food aversion was hypothesised due to an initial decrease in food consumption during the first few days of feeding in P1 animals. However, it resulted in a significant decrease in food consumption during the first week in high-dose males only and was not associated with noticeable clinical signs. It was suspected that rats then have acclimated to the test-substance in the diet. In relation to postnatal delay in growth, pups progressively start to consume solid food from their second week of life and during this period measured food consumption covers both the dams and the pups consumption so that pup consumption cannot be determined. However, the decrease in food consumption during lactation was much lower than the decrease in pup weight at PND21. In the highest-dose group, it reaches only -17% of food consumption vs -28% of pup bodyweight in F1 and -7% of food consumption vs -28% of pup bodyweight in F2. It is therefore difficult to attribute the postnatal effects to food aversion.

It is not known whether RDP or its metabolites are present and can accumulate in the milk. The impurity TPP was detected in human breast milk in a cohort conducted in Sweden between 1997 and 2007. Median concentration was 8.5 ng/g of lipids (minimum and maximum values: 3.2 and 11 ng/g, respectively) (Sundkvist et al., 2010). Toxicokinetic data in the rat indicate that RDP or its metabolites are present in higher concentration in the mesenteric fat than in the residual carcass further to a single exposure via iv route. It is however not known whether it can result in accumulation in fat after repeated exposure.

A possible effect on lactation in the dams could also be hypothesised. In the two-generation study (Henrich et al., 2000b), dams of both generations exhibited increased adrenal weights from the low dose (1000 ppm, approx. 55 mg/kg/d) and adrenals hormones are known to influence prolactin (Harvey et al., 2007).

In humans, associations have been found between higher corticosteroids levels and decreased milk production, delay or difficulty in breast feeding (Babwah et al., 2013; Henderson et al., 2008; Karakoyunlu et al., 2019; Grajeda and Pérez-Escamilla 2002; Chen et al., 1998 ; Caparros-Gonzales et al., 2019). Corticosteroids are produced in the adrenal cortex and the observed effects may have consequences on their synthesis. However, data to investigate a possible link are not available. No information is available to support or dismiss an effect on milk production but it is noted that pup bodyweight were not affected during the first week of lactation.

No adverse effects was observed on any reproductive or fertility parameter measured (sperm parameters, estrous cycles, number of follicles, reproductive performance).

Consistent findings are observed across generations in this two-generation dietary study (Henrich et al., 2000b). Affected organs in adults are the liver and the adrenals. The relative increase in the weight of male reproductive organs (testis, epididymis and cauda epididymis) is not accompanied by histopathological changes and sperm parameters are unaffected. Reproductive function and performance is also not altered by dietary exposure to RDP.

An irreversible delay in pup growth after birth is reported in both F1 and F2, as evidenced by a reduction of body growth and a delay in developmental landmarks (vaginal opening and preputial separation). Food consumption was also transiently altered but not during all periods of exposure so that an aversion to food cannot explain the effect on offspring development. Overall, it provides some evidence of a post-natal developmental effect that warrants consideration as an adverse effect in the NOAEL setting. An increase in brain weight is also noted.

7.9.7.2. Developmental studies

A prenatal toxicity study (equivalent to OECD TG 414) was conducted in New-Zealand white rabbits (Ryan et al., 2000). Fyrolflex RDP (TPP content of 4.7%) was administered by gavage in corn oil at doses of 50, 200 or 1000 mg/kg/ from gestation days (GD) 6-28. No maternal toxicity was observed. No mortality was attributed to treatment, no clinical signs and no significant effect on body weight, food consumption or organ weight were observed although occasionally increased bodyweight gains and food consumption were observed in the high-dose group. Thyroid was not weighted and histology was not performed but no gross abnormalities was observed.

No effect was observed on fetal bodyweight or viability. The sporadic observation of rare cephalic malformations was reported, in particular 2 fetuses in two litters at the high dose had convoluted lens (historical control data: 0 in 672 fetuses from 97 litters), one high dose fetus had an ectopic lens and one fetus from the mid- and the high-dose groups had dilated ventricles. Ossification of the skull was not altered.

A prenatal toxicity study (performed according to OECD TG 414) was conducted in Sprague-Dawley rats (Unpublished report 2019d). Fyrolflex RDP (TPP content of 4.4%) was administered by gavage in corn oil at doses of 40, 200 or 1000 mg/kg/ from GD 6-19. Satellite groups (n=10/group) were added to measure ChE activities as well as an additional control group to generate historical control data for ChE measurement in pregnant dams.

Regarding maternal toxicity, no mortality was attributed to treatment, no clinical signs (except salivation) were observed. A significantly increased bodyweight was observed on GD20 as well as transient increased in food consumption at the highest dose. This was however due to an increased gravid uterine weight and corrected maternal bodyweight was unaffected. No effect was observed in brain ChE activity whereas decrease of plasma ChE activity was significant from low dose. The decrease of erythrocyte ChE activity from mid-dose was significant only compared to one of the two control groups. Absolute brain weight was decreased in the high-dose group although corrected bodyweight was similar across groups but it was significant only when compared to one of the two control groups. Thyroid was not weighted and histology was not performed but no gross abnormalities was observed.

Regarding fetal toxicity, no significant effect was observed on fetal bodyweight or viability. In the high-dose group, the number of foetuses per litter and fetal weight were slightly higher but not significantly. No effect was observed in brain and erythrocyte ChE activities and no clear decrease of plasma ChE activity was observed as it was significant only when compared to one of the two control groups. Malformation incidences were not noticeable

compared to the historical control database. Ossification of the skull was not altered. A variation in lens shape was observed in 2 fetuses both at the mid- and high-doses but historical controls were 0 to 5 fetuses.

Conclusion: The prenatal toxicity studies by gavage in rabbit and rats do not indicate developmental effects.

7.9.8. Neurotoxicity

7.9.8.1. In vitro study

RDP has been developed as a substitute of brominated flame retardants that affect the nervous system and similar effects are suggested for non-halogenated flame retardants such as TPP and an in vitro neurotoxicity study was conducted with RDP. The cytotoxicity and production of Reactive Oxygen Species (ROS) was measured in rat pheochromocytomas cells (PC12) and rat neuroblastoma (B35) cells exposed to 0.01 to 100 µM of RDP (purity > 95% TPP 4-5%) in DMSO (Hendricks et al., 2014). It is noted that as PC12 cells were not differentiated into glial or neuronal cells before exposure, this study provides information on the cytotoxic potential of the substance but not on its neurotoxic potential. Changes in the intracellular calcium concentration was also measured in PC12 cells. TPP was also tested.

No effect was observed on the viability of PC12 and B35 cells up to the highest concentration. No induction of ROS was observed, in contrast to TPP (increase of ROS in B35 cells ≥ 1 µM) and no effect on basal [Ca2+] in PC12 cells (effect of TPP at 100 µM) but a reduction of depolarization-evoked increase in [Ca2+] was seen from 1 µM (effect of TPP from 1 µM). Effects of TPP and RDP were in the same range of concentration, so the effect of RDP cannot be attributed to the presence of TPP as an impurity. It was noted by the authors that TPP-like compounds may be formed as breakdown products in culture media.

An agonist activity was observed on the nicotinic acetylcholine receptor (nACh-R) at the highest concentration of 100 µM and from 1 µM with TPP and the activity of RDP on n-Ach-R may be caused by the presence of TPP as an impurity.

7.9.8.2. Studies in hens

RDP (purity unknown) was administered by gavage to 20 adult hens at a dose of 5 000 mg/kg on day 1 and on day 21 (Unpublished report 1989a). The study was terminated on day 42. No death occurred and no overts clinical signs were reported including during daily forced motro activity observation. Hens lost weight between day 1 and 21. No histopathological findings were reported in brain, spinal cord and sciatic nerves.

Fyrolflex RDP (TPPO 4.7%) was administered neat by gavage to 10 adult hens for 5 days at a dose of 2000 mg/kg (Unpublished report, 1994c). No death occurred and no overts clinical signs were reported. Hens lost weight during the study course. The decrease of neurotoxic esterase activity was of minimal (14%).

Fyrolflex RDP (TPPO 4.7%) was administered neat by gavage to 8 adult hens for 5 days at a dose of 2000 mg/kg (Unpublished report, 1994d). Similarly to previous study, no death occurred and hens lost weight during the study course. The decrease of neurotoxic esterase activity was of 11% and considered negligible (criterion of 70% for positivity).

RDP (purity unknown) was administered as a single dose of 5000 mg/kg to hens. Plasma cholinesterase was significantly depressed 24, 48 and 72 hours post-dosing and had almost returned to baseline levels 7 days after dosing, representing recovery. No treatment related effect was noted on whole blood or red blood cell cholinesterase.

7.9.8.3. Studies in rats

A number of acute studies have investigated ChE activities.

- In an acute inhalation study (Unpublished report 1994d), aerosolised Fyrolflex RDP (monomer 65-80%, TPP<5%) was administered SD rats for 4 hours at a concentration of 4.14 mg/l. No mortality, no effect on body weight and no clinical indicative of neurotoxicity were observed. MNSE activity was significantly decreased on the day after exposure (70% of pre-test value). After 14 days, Monocyte Non-Specific Esterase (MNSE) activity was not significantly modified (128% of control).

- Neurotoxicity of Fyrolflex RDP (purity not known) was investigated in a series of acute oral toxicity study, in which MNSE activity was also determined. Rats were exposed to a dose of 5000 mg/kg and observed for 14 days.
  - In ESR 007 and ESR 011, decrease of MNSE activity was not observed at day 1 or 14 days after exposure.
  - In ESR 008, no significant effect on MNSE activity was observed at day 1 (134% of pre-test control) but a significant decrease was observed on day 14 after exposure (71% of control).
  - In ESR 009, plasma and whole blood ChE activities were decreased up to 72 hours post dosing in females. No effect was observed in males.

- In an acute dermal study, in rats exposed to 2000 mg/kg (ECHA disseminated website, ESR 010, study report not consulted), no significant effect on MNSE activity was observed at day 1 (96% of pre-test control) but a significant decrease was observed on day 14 after exposure (63% of control).

In addition, ChE activities have been measured in the repeated-dose and reproductive toxicity studies reported above.

All parameters relevant for neurotoxicity in the whole database are summarised in the table below.

7.9.8.4. Conclusion

Overall, RDP decreases plasma ChE activity but no clear effect is observed on erythrocyte or brain ChE. *In vitro*, RDP was however able to reduce the depolarisation-evoked increase in [Ca2+]. No neurotoxic clinical signs were induced in the different studies of the database and sensory and motor activity were not altered by RDP in the 90-day gavage study. These data do not raise a concern for a direct neurotoxic potential.

Follicular cell hypertrophy in the 90-day study may indicate an effect on the thyroid. In addition, RDP can be metabolised into resorcinol, a known inhibitor of the thyroid peroxidase (TPO). Alteration of thyroid hormones that may result from TPO inhibition can have consequences on the neurodevelopment of the offspring (adverse outcome pathway n°42[2]) (see also section 7.10.2 on assessment of ED properties). The effect of RDP on neurodevelopment has not been tested in any study.

[2] https://aopwiki.org/aops/42

Table 23 – Summary of experimental *in vivo* findings in relation to the neurotoxic potential of RDP

Study reference	Design	Test material and purity	Esterase activity						Clinical/ behavioural signs	Organ weight, histo
			Plasma ChE	Erythro ChE	Whole blood ChE	MNSE	Brain ChE	NTE		
Hens studies										
Unpublished report 1989a	Hens, gavage on day 1 and 21, 5000 mg/kg	Fyrolflex RDP	ND	ND	ND	ND	ND	ND	No effect	No histo findings in brain, spinal cord and sciatic nerve
Unpublished report 1994c	Hens, 5-day gavage, 2000 mg/kg	Fyrolflex RDP TPPO 4.7%	ND	ND	ND	ND	ND	=	No effect	ND
Unpublished report 1994d	Hens, 5-day gavage, 2000 mg/kg	Fyrolflex RDP TPPO 4.7%	ND	ND	ND	ND	ND	=	No effect	ND
ECHA website, ESR 012	Hens, acute, oral, 5000 mg/kg	CR733S	↘ (up to 72 h)	=	=	ND	ND	ND	ND	ND
Rats, acute studies										
Unpublished report 1994c	Rats, acute, inhalation,	Fyrolflex RDP (TPP<5%)	ND	ND	ND	↘ (day 1 but not day 14)	ND	ND	No effect	ND
ECHA website, ESR 007	Rats, acute, oral, 5000 mg/kg	Fyrolflex RDP	ND	ND	ND	=	ND	ND	ND	ND
ECHA website, ESR 008	Rats, acute, oral, 5000 mg/kg	Fyrolflex RDP	ND	ND	ND	↘ (day 14 but not day 1)	ND	ND	ND	ND

ECHA website, ESR 009	Rats, acute, oral, 5000 mg/kg	Fyrolflex RDP	↘ (F, up to 72 h)	ND	↘ (F, up to 72 h)	ND	ND	ND	ND	ND
ECHA website, ESR 011	Rats, acute, oral, 5000 mg/kg	Fyrolflex RDP	ND	ND	ND	=	ND	ND	ND	ND
ECHA website, ESR 010	Rats, acute, dermal, 2000 mg/kg	Fyrolflex RDP	ND	ND	ND	↘ (day 14 but not day 1)	ND	ND	ND	ND
Rats, repeated-dose studies										
Henrich 2000a	Rats, 28-day, inhalation, 0, 0.1, 0.5, 2 mg/l	Fyrolflex (TPP<5%)	↘	=	ND	↗	ND	ND	No effect	No effect
Unpublished report 2019	Rats, 90-day, gavage, 0, 30, 100, 300, 1000 mg/kg	Fyrolflex RDP (TPP<5%)	↘	↘ (high dose F)	ND	ND	=	ND	No effect on sensory reactivity, grip strength and motor activity (wk 12)	No effect
Unpublished report 1989b	Rats, 28-day, IP, up to 500 mg/kg	CR733S	↘	ND	ND	↘	ND	ND	No effect	No effect
Unpublished report 1990	Rats, acute, IP, 500 mg/kg	CR733S	↘	=	ND	ND	ND	ND	No effect	No effect
Henrich 2000b	Rats, 2-generation, diet, approx. 0, 55, 600, 1200 mg/kg	Fyrolflex RDP	ND	ND	ND	ND	ND	ND	No effect	↗ rel. brain wt (M all doses, F low and high doses) No histo exam.
Unpublished report 2019	Rats, GD 6-19, gavage, 0, 40, 200, 1000 mg/kg	Fyrolflex RDP (TPP 4.4%)	Dams: ↘ Fetuses: ↘ (eq)	↘ (eq) =	ND	ND ND	= =	ND	No effect	Dams: eq. ↘ abs. brain wt (high dose) No histo exam.

NTE: neuropathy target esterase; ND: no data; eq: equivocal; M: male; F: female

7.9.9. Immunotoxicity

Because an effect on monocyte activity was observed on similar organophosphorus compounds, a 28-day study was performed to investigate potential immunotoxicity of RDP (Sherwood et al., 2000). Fyrolflex RDP (purity not known) was administered neat by gavage to female B6C3F1 mice (n=10/group/endpoint) at doses of 500, 1500 or 5000 mg/kg/d. Tests were performed at the end of the exposure period and after an additional 60-day recovery period.

No histopathological changes were observed in the thymus, spleen, mesenteric, mediastinal and mandibular lymph nodes and no effect was seen on spleen and thymus cellularity. High-dose females were slightly but significantly heavier than controls at the end of exposure. This effect was not observed at any time point in the recovery period.
No effect was observed on erythrocyte ChE activity. A significant and dose-related decrease in plasma ChE activity was observed after 28 days of exposure in all RDP-treated groups. The activity was similar to controls after 60 days of recovery.

No effect was observed on the number of peritoneal cells and cell types, no significant effect on the phagocytic activity as measured by the percent of viable peritoneal macrophages having ingested at least one bead and by the mean number of beads per cell when incubated in non-supplemented media, augmentative (lipopolysaccharides) or inhibitive (demecolcine) media in presence of latex beads. No significant effect was observed on splenic natural-killer cell activity (basal and rhIL-2 augmented), on lymphocyte blastogenesis induced by α-CD3 antibody or on splenic lymphocyte antibody plaque-forming cell response. No significant effect was seen on the susceptibility to infection to L. monocytogenes (% mortality and survival time). Positive controls (cyclophosphamide or diethylstilbestrol) gave appropriate responses in all assays.

No immunotoxic potential was detected up to 5000 mg/kg for 28 days in mice and no alert was observed in the other studies of the database. Based on this data, no further investigation is considered necessary.

7.9.10. Hazard assessment of physico-chemical properties

Not evaluated during SEv.

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

Not evaluated during SEv.

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

RDP induces an increase in liver weight by oral and inhalation routes and minimal to slight hypertrophy is observed in the 90-day gavage study. Lungs are also affected after 28 days of exposure by inhalation (persistent increase in weight and alveolar histiocytosis progressing in chronic body foreign inflammation).

In the 90-day gavage study, RDP also induces follicular cell hypertrophy in the thyroid. An increase in the adrenals weight is observed in the 90-day study and in the two-generation study with a higher sensitivity of females. These effects are further discussed in section 7.10.2 dedicated to the ED assessment.

Available data on the direct neurotoxic and immunotoxic potential of RDP do not raise concern and further investigation of these properties are not considered necessary.
RDP does not affect fertility nor development during gestation but a marked delay in postnatal growth of pups during the lactation period is observed in both F1 and F2 pups in

the two-generation study, with consequences on developmental landmarks (vaginal opening and preputial separation). Whether a contribution to this effect can be related to food aversion, effect on or via lactation or other modes of action (including ED modes of action) is not elucidated.

However, data are awaited on the ED potential of TPP and regulatory actions are under consideration for resorcinol. These data and actions may result in risk management measures for RDP and further tests are not requested for RDP at this stage. This conclusion will be reconsidered when the awaited data on TPP and outcome of regulatory actions for resorcinol will be available, depending on their results.

7.10. Assessment of endocrine disrupting (ED) properties

7.10.1. Endocrine disruption – Environment

There is no available data on the endocrine disrupting properties of RDP. However, the ED properties of metabolites are considered below.

7.10.1.1. TPP

TPP has shown an *in vitro* potential of endocrine-disrupting effects via ERα / ERβ, AR, GR, and PXR activity.

Also, there is evidence that TPP could interfere with endocrine systeme *in vivo*. The observed effects indicate an estrogenicity of TPP in female and male zebrafish, with increased plasmatic concentrations of E2 and, in some cases, of VTG. Decrease in plasmatic concentrations of 11-ketotestosterone in both sexes of fish were also observed. Moreover, in zebrafish and Japanese medaka, TPP had a negative effects on the egg number and their hatchability in a dose- and time- dependent manner. Sex-dependent changes in transcriptional profiles of several genes of the hypothalamic-pituitary-gonad (HPG), hypothalamic-pituitaryinterrenal (HPI) and hypothalamic-pituitary-thyroid (HPT) axes where also observed. In particular, *erα*, *trh, fshβ, T3, T4* were genes whose expression was modulated after exposure to TPP (ANSES, 2019).

In that regard, there is an on-going evaluation of TPP for its endocrine disrupting properties for the environment.

7.10.1.2. Resorcinol

There is evidence that Resorcinol has ED properties impacting the thyroid gland function, especially the thyroid hormones. It was reflected by the decrease of intrafollicular T4 content in zebrafish eleutheroembryos (Thienpont *et al*. 2011) and recently highlighted again by data from a screening study (Jarque *et al*., 2018), indicating that resorcinol induces fluorescence in thyroid gland of specifically genetically modified zebrafish eleutheroembryos for detection of ED compound. Resorcinol is considered able to disturb thyroid hormone synthesis through inhibition of the TPO. These data highlight the individual effects of resorcinol on thyroid gland function, but do not provide indication on potential effects at the population level.

In that regard, there is an on-going evaluation of resorcinol for its endocrine disrupting properties for the environment.

7.10.2. Endocrine disruption - Human health

The activity of RDP for estrogen and androgen receptor was modelled in respectively the CERAPP (Collaborative Estrogen Receptor Activity Prediction Project- See Mansouri et al. 2016) and the CoMPARA (Collaborative Modeling Project for Androgen Receptor Activity- See Mansouri et al. 2020) projects that combine several QSAR modelling and docking approaches.

For RDP, results were as follows (source US EPA website[3]):

Table 24 - Summary of RDP modelled affinity towardestrogen and androgen receptors

Model	Receptor	Agonist	Antagonist	Binding
COMPARA	Androgen	Inactive	Active	Active
CERAPP Potency Level (Consensus)	Estrogen	Inactive (Inactive)	Inactive (Inactive)	Active (VeryWeak)

The ED properties of RDP have not been specifically investigated *in vivo*. From the repeated-dose and reproductive toxicity effects described above, the following effects are noted on endocrine organs or ED-sensitive parameters:

- Increased body weight may indicate metabolic disturbance

Body weight was increased in high-dose females during recovery in the 28-day inhalation study and occasional increases in bodyweight gain and food consumption in high dose dams were reported in the rabbit prenatal study. Body weight of females was also higher at the end of the 28-day immunotoxicity study (gavage, 5000 mg/kg). However, no effect on triglycerides or cholesterol was observed in the different studies and no clear pattern effect on glucose in blood was noted.

- Increased weight of some male reproductive organs in P1 and F1 males of the two-generation study

However, no effect was observed on histology, sperm parameters and reproductive performance.

- Effect on adrenals weight

No effect was observed in the 28-day inhalation study. The relative weight was increased at all doses (from 30 mg/kg/d) in females in the 90-day gavage study but no histological findings were reported (only 10/20 animals examined in the control and high-dose groups) and the relative weight was increased in males (≥ mid-dose, approx. 600 mg/kg/d) and females (all doses, from approx. 55 mg/kg/d) in P1 and F1 of the two-generation dietary study (histology not performed). The effect was attributed by the authors of the study to stress related to food aversion (Henrich et al., 2000b). However, this conclusion is not further substantiated and other modes of action can be involved. The effect is more pronounced in females.

In males, cellular proliferation is inhibited by testosterone and DHT in the adrenal cortex (Grabeck et al., 2019), resulting in a larger adrenal glands in females than in males. This physiological difference can also explain the lesser sensitivity of males in relation to change in adrenal size. In the hypothesis of an effect on glucocorticoids, it is expected to be associated with changes in glucose levels in blood. This parameter has not been measured in the two-generation study. In the 90-day study, a decreased in glucose in blood was observed in males from 100 mg/kg but not in females and no clear conclusion can be made.

- Alteration of thyroid

No effect is reported on either thyroid weight or histology in the 28-day inhalation study. However, follicular hypertrophy was observed in the 90-day gavage study in males and females with a dose-related incidence and/or severity. Thyroid hormone measurements are not available in any study.

[3] https://comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID8069197#bioactivity

- Postnatal developmental delay in growth and associated landmarks in the two-generation study

Whether a contribution to this effect can be related to food aversion, effect on or via lactation or other modes of action including ED modes of action such as thyroid or glucocorticoid disruption is not elucidated.

In addition, ED properties of metabolites are considered.

- TPP

TPP (ANSES, 2019) has shown an *in vitro* potential of endocrine-disrupting effects via ERα / ERβ, AR, GR, and PXR activity. Some evidence that exposure to TPP may be associated with increased total thyroxine levels in Humans (especially in women). Finally, metabolic disturbance after perinatal exposure (Green et al., 2017, Patisault et al., 2013) is reported.

- Resorcinol

There is scientific evidence that resorcinol can have adverse effects on human health through thyroid disruption and fulfils the definition of an endocrine disruptor (ECHA, 2019): Resorcinol is able to disturb thyroid hormone synthesis through inhibition of the thyroid peroxidase (TPO). Due to efficient metabolism, resorcinol is quickly metabolised after its production from RDP. However, it has been detected as one of the main urinary metabolites in the mouse, the monkey and the rat (Freudenthal et al., 2000), with urinary route of excretion being a more important in primates than in rodents. Besides, resorcinol was shown to be a potent TPO inhibitor *in vitro* so that low systemic levels may be relevant to consider in the assessment of ED properties of RDP.

Kojima et al. (2016) have demonstrated that mono-hydroxylated metabolites (common metabolites of RDP and TPP) have ERα, ERß and PXR agonist activity and ERß, AR and GR antagonist activity (transcriptional activity on human nuclear receptors) *in vitro*. The most potent activity was toward ERα and ERß (agonist) (REC_{20} of 4-OH-TPP for ERα= 0.29 µM). Metabolites were more potent estrogenic compounds than the parent compound TPP and it can be speculated that potential endocrine disrupting effects of TPP and RDP could be mediated by these metabolites.

Conclusion

The metabolism of RDP into resorcinol, a known thyroid disruptor, together with the induction by RDP of follicular cell hypertrophy in the 90-day gavage study raise a concern on thyroid disruption by RDP. The indication of an effect of TPP (impurity of RDP that share similar metabolites) on thyroid hormones in human also supports the concern. Further investigation are therefore required to clarify the thyroid-disrupting potential of RDP.

An effect on adrenals weight in two oral studies, together with indication of an activity of RDP metabolites on the glucocorticoid receptor also require further investigations to be clarified.

Based on the available data, the endocrine disruptive potential can neither be confirmed nor excluded. Although other modes of action are possible, it cannot be excluded that the delay in postnatal growth observed in the two-generation study can be explained at least partly by the potential ED properties of RDP, in particular on thyroid and/or adrenals.

The elements relevant for the identification of a substance as an ED according to the WHO/ IPCS definition (2002) are summarized in Table 25 below.

Table 25 - Summary of elements relevant for ED identification

Lines of evidence of an endocrine activity	
• Thyroid follicular hypertrophy in the 90-day study. • The urinary metabolite resorcinol is a potent TPO inhibitor. Its presence in blood is unknown. • The impurity TPP is associated with decreased T4 in some human studies. **➔ Indications of a thyroid activity that have not been clarified**	• Increased adrenal weight, in particular in females. • Activity of the impurity TPP on GR. **➔ Indications of an adrenal activity that have not been clarified**
Lines of evidence of an adverse effects	
• Effect on growth during or via lactation	
Plausibility of the link between endocrine activity and adverse effects	
• Plausibility of the link between thyroid activity and an effect on growth via or during lactation is uncertain based on available data. • The effects plausibly linked and more sensitive to thyroid disruption have not been investigated (e.g. neurodevlopment).	• Plausibility of the link between adrenal activity and an effect on growth via or during lactation is uncertain based on available data. • The effects plausibly linked and sensitive to adrenal disruption have are not specifically defined in the regulatory framework.

7.10.3. Conclusion on endocrine disrupting properties (combined/separate)

Based on available data, the endocrine disruptive potential of RDP can neither be confirmed nor excluded.

However, data are expected on the ED potential of TPP and regulatory actions are under consideration for resorcinol. These data and actions may indirectly result in risk management measures for RDP. Therefore, it does not appear appropriate at this stage to request complex animal studies for RDP, in particular for thyroid. This conclusion shall be reconsidered when the expected data on TPP and outcome of regulatory actions for resorcinol will be available, depending on their results. Besides, there are no available (or limited) guidelines or validated animal models to explore the effects related to adrenal hormones. European research projects (EURION[4] cluster of projects) are on-going and may provide in the future information on what are the relevant parameters to investigate these effects.

7.11. PBT and VPVB assessment

Persistence assessment

There is multiple evidence on potential degradability, ready biodegradability (OECD TG 301 D, 61 % in 28 days) and screening test with longer test duration (OECD TG 301 D, 66 % in 56 days) leading to the conclusion that RDP seems not to meet the P/vP criteria.
Conclusion on P / vP properties: not P/vP

[4] https://eurion-cluster.eu/

Bioaccumulation assessment

Based on the results of a read-across and modelisation, RDP does seem to be bioaccumulative (B) or very bioaccumulative (vB).
Conclusion on B / vB properties: not B/vB

Toxicity Assessment

Based on the results from a chronic daphnia toxicity (OECD TG 211, NOEC of 21 µg/L), RDP is considered as not toxic (T) for the environment.
Conclusion on T properties: Fyrolflex not T

Overall conclusion

Based on the available data, RDP is not a PBT or vPvB, according to Annex XIII of REACH.

7.12. Exposure assessment

7.12.1. Human health

7.12.1.1. Worker

A review (van der Veen & de Boer, 2012) mentions evidence that RDP-containing fumes and aerosols are released during the application of RDP at production sites but no further information or reference is provided to support this statement.

7.12.1.2. Consumer

RDP has been detected in dust samples from houses in several countries including the Netherlands, Greece, Sweden, UK, Spain, Australia and China, offices in the Netherlands and in UK and classrooms in Spain (Brandsma et al., 2013, Ballesteros-Gomes et al., 2016, Kademoglou et al., 2017, Sugeng et al., 2017, Tan et al., 2018, Li et al., 2019, Dueñas-Mas et al., 2020, Huang et al., 2020) and in some dust samples collected in cars in the Netherlands, in Sweden and in Greece (Brandsma et al., 2013, Christia et al., 2018).

Electronic equipment is hypothesised as the source of RDP present in indoor dust (Brandsma et al., 2013), in particular when electronics equipment is recently produced (Sugeng et al., 2018). The presence of RDP in plastics from electronic products is reported by Ballesteros-Gomes et al. (2014) with data suggesting an increased frequency of detection in recent years but at lower concentrations.

Hydrolysis products such as DPHP are also detected (Bjorsdotter et al., 2015, Ballesteros-Gomes et al., 2016, Huang et al., 2020), although they may also come from other flame retardants such as BPA-BDPP or TPP. These flame retardants are commonly used in mixture with RDP. RDP is also detected in children's car seats in the US (Wu et al., 2019).

The potential of human exposure to RDP is further demonstrated by its detection on the hand of toddlers collected in the Netherlands via hand wipes (Sugeng et al., 2017, Sugeng et al., 2020) and for adults and toddlers in China (Tan et al., 2018). Children with more frequent hand-to-object behavior had significantly more often levels above the level of detection (LOD) ($p<0.002$) and children living in houses that were renovated less recent had higher levels on hand as collected via wipes ($p<0.015$) (Sugeng et al., 2020).

Finally, RDP was detected in respectively 18% (range: <0.27-5.36 ng/ml), 0% and 10% of the samples (range: <0.054–0.078 ng/ml) from 52 paired whole blood, serum and urine samples collected in Beijing (China). DPHP that is formed from RDP as well as from multiple other organophosphate flame retardants was detected in all whole blood and urine samples and in 61% of serum samples (Hou et al., 2020).

Table 26 - Summary of main data investigating presence of RDP in dust, plastics, body wipes or biological samples

Media	Country	Frequency of detection	Median (range)	Comments	Reference
House dust Car dust	Netherlands Greece Sweden Netherlands Sweden	5/8 (63%) 3/5 (60%) 3/3 (100%) 1/8 (12.5%) 4/4 (100%)	(<30-52 000 ng/g) (<30-4 400 ng/g) 39 (25-97 ng/g) (<1.1-34 000 ng/g) (8.1-220 ng/g)	Concentrations higher in samples form the electronics	Brandsma et al., 2013
Plastics	Netherlands	4/13 (30%) 7/12 (58%)	0.005 to 7.8% w/w 0.002–0.3% w/w	Purchased in 1998-2006 Purchased in 2012	Ballesteros-Gomes et al., 2014
Indoor dust	Netherlands Spain	1/23 (4.3%) 0/57 (0%)			Bjornsdotter et al., 2018
Plastics Indoor dust	Netherlands Netherlands	10/25 (40%) 25/30 (83%)		Purchased in 2015	Ballesteros-Gomes et al., 2016
House dust House dust Store/office dust	Norway UK UK	0/10 (0%) 5/10 (50%) 12/12 (100%)	(<1.8 ng/g) 1.9 (<1.8-3.1 ng/g) 6.1 (2.0-53.5 ng/g)	Collected in 2013/2014	Kademoglou et al., 2017
House dust Body surface	Netherlands Netherlands	43% 87%	34 (11-1 792 ng/g) 0.3 (0.1-4 ng/wipe)	– Toddlers	Sugeng et al., 2017
House dust	Netherlands	40/50 (80%)	32 (2.1-1 792 ng/g)		Sugeng et al., 2018
Car dust	Greece	7/25 (28%)	4 (4-646 ng/g)		Christia et al., 2018
House dust Hand surface	China China	94% 15%	0.06 (<LOQ-1560 ng/g) (<LOQ-22.8 ng)	Adults	Tan et al., 2018
Baby's car seat	USA	4/18 (22%)	6.15 µg/g (<LOD – 5 020 µg/g)		Wu et al., 2019
House dust	12 countries	47% (160/341)	(<LOD-5480 ng/g)	Collected in 2010-2014	Li et al., 2019
House dust Classroom dust	Spain Spain	11/22 (50%) 13/16 (81%)	(<LOD – 166 ng/g) 14 (<LOD – 317 ng/g)		Dueñas-Mas et al., 2020
Hand surface	Netherlands	29/49 (59%)	0.06 (0.03 - 3.34 ng/wipe)	Toddlers	Sugeng et al., 2020
House dust	Australia	31/43 (72%)	85.1 (<LOD – 643 ng/g)		Huang et al., 2020
Whole bl. Serum Urine	China China China	18% 0% 10%	(<0.27-5.36 ng/ml) - (<0.054–0.078 ng/ml)		Hou et al., 2020

7.12.1.3. Summary

Human exposure has not been characterised in details during the SEv. However, data available from the literature indicate that the general population is exposed from dust.

Presence of RDP in dust is associated with its increasing use as a flame retardant in electronic equipments. RDP has also been detected in baby's car seat in the US (Wu et al., 2018) and in toys and pacifiers in the Netherlands (Ballesteros-Gomes et al., 2014).

7.12.2. Environment

7.12.2.1. Aquatic compartment (incl. sediment)

Matsukami et al. (2017) investigated the concentrations of OPFRs in surface soils and river sediments from an informal e-waste-processing area in Bui Dau (Hung Yen Province, northern Vietnam) for the period 2012-2014 (see 7.8.1 for sediment data). They collected surface soil samples (depth 0-5 cm) from footpaths in rice paddy sites (n=19), near the open-burning sites (n=3), and near the e-waste-processing workshop sites (n=10) in January 2012. The samples collection was perfomed again in 2013 and 2014, leading to a total of 96 soil samples. Samples were analysed by LC-ESI-MS/MS, LC-APPI-QTOF-MS and GPC. RDP median concentrations in the rice-paddy site and the open-burning site were always below the LOD (0.7 ng/g) but increased in the e-waste processing site from 350 to 770 ng/g. TPP median concentrations in the rice-paddy site and the open-burning site were always below the LOD (0.7 ng/g, except in 2013 for the open-burning site with a median concentration of 7.3 ng/g) and increased at the e-waste processing site from 110 to 720 ng/g. The median concentrations for RDP and TPP at the e-waste processing sites increased by up to 2 and 6 folds, respectively.

The authors then determined the environmental emission of oligomeric PFRs and observed evolution between 2013 and 2014. They observed that the ratio for degradation products and technical formulation of RDP suggest that increased in median concentrations of HP-DPHP (3-hydroxyphenyl diphenyl phosphate) arise from instability of RDP.

Matsukami et al., 2015, investigated the concentrations of FRs in surface soils and river sediments (experiment and material and method identical than previous described study). RDP concentration in the rice-paddy site (DF=5%) was 7.3 ng/g, <LOQ (0.7 ng/g) to 1.1 ng/g (DF=33%) in the open-burning site and between 6.6 to 14000 ng/g (DF=100%) in the e-waste processing site. TPP concentration in the rice-paddy site (DF=5%) was comprised between <LOQ (3 ng/g) to 10 ng/g, <LOQ to 51 ng/g (DF=33%) in the open-burning site and between 11 to 3300 ng/g (DF=100%) in the e-waste processing site. The highest concentration of RDP was found in site of the e-waste processing site where open storage of large amounts of e-waste such as cathode ray tubes, electronic housings, and printed circuit boards around the roadside were observed. The authors hypothetised that open storage of e-waste is an important source of environmental contamination by FRs.

7.12.2.2. Terrestrial compartment

No relevant information available

7.12.2.3. Atmospheric compartment

No relevant information available

7.12.3. Combined exposure assessment

Not further characterised.

7.13. Risk characterisation

7.13.1. Human health

Not further characterised.

7.14. References

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7.15. Abbreviations

ANSES: French Agency for Food, Environmental and Occupational Health & Safety
AR: androgen receptor
AUC: area under the curve
CERAPP: Collaborative Estrogen Receptor Activity Prediction Project
ChE: cholinesterase
Cmax: maximal concentration
CoMPARA: Collaborative Modeling Project for Androgen Receptor Activity
CYP: cytochrome P
DHT: dihydrotestosterone
DMEL: derived minimal effect level
DMSO: dimethyl sulfoxide
DNEL: derived no effect level
DPHP: diphenyl phosphate
ECHA: European Chemicals Agency
ED:endocrine disruption
eMSCA: evaluating Member State Competent Authority
ER: estrogen receptor
ESR: endpoint study report
GD: gestation day
GR: glucocorticoid receptor
IP: intraperitoneal route
Iv: intravenous route
LOD: level of detection
MMAD : median mass aerodynamic diameter
MNSE: monocyte nonspecific esterase
nACh-R: nicotinic acetylcholine receptor
ND: no data
NTE: neuropathy target esterase
OECD: Organisation for EconomicCo-operation and Development
PEG-400: polyethylene glycol-400
PND: postnatal day
PXR:pregnane X receptor
RDP: Resorcinol bis-diphenylphosphate or Tetraphenyl m-phenylene bis(phosphate)
REC20: 20% relative effective concentration
ROS: Reactive Oxygen Species
SD: Sprague-Dawley
SEv: substance evaluation
T1/2: half-life
TG: technical guideline
Tmax: time of maximal concentration
TPP: triphenylphosphate
TPO: thyroid peroxidase
UK: United Kingdom
US EPA: United States Environmental Protection Agency