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Analysis of the most appropriate risk management option (RMOA)

Substance Name: tetraphenyl m-phenylene bis (phosphate)

EC Number: 260-830-6

CAS Number: 57583-54-7

Authority: France

Date: March 2017

Cover Note

This chemical (tetraphenyl m-phenylene bis (phosphate – RDP) is presented by industry as a potentially viable alternative to decabromodiphenyl ether (decaBDE) in a variety of polymers and applications.

RDP exists in multiple forms: the n=1 (tetraphenyl m-phenylene bis (phosphate) CAS No 57583-54-7 as multi-constituents substance), and n=2 oligomers are those with a MW <1,000.
The material used by industry (commercial RDP) for flame retardant applications is most likely the polymeric material (with CAS number: 125997-21-9), although the CAS number for the discrete organic where n=1 (CAS No 57583-54-7) has been used interchangeably with 125997-21-9 in the publicly available literature. The monomeric form (CAS No 57583-54-7) is, however, most likely to be released from flame fireproof materials.

The RDP is suspected to be an endocrine disrupter (ED) substance because of a warning in a Two generations study, in which a delay in preputial separation and vaginal opening was observed at the two highest tested dose levels. This study was conducted on:

- SD rats (30 per sex and per dose) exposed at commercial RDP (0, 50, 500, and 1000 mg/kg bw/d)
- In F1 (observations at 28-45 PND for males, and at days 34-55 PND for females), a delay in preputial separation and vaginal opening has been observed at the two highest tested dose levels.

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1 IDENTITY OF THE SUBSTANCE

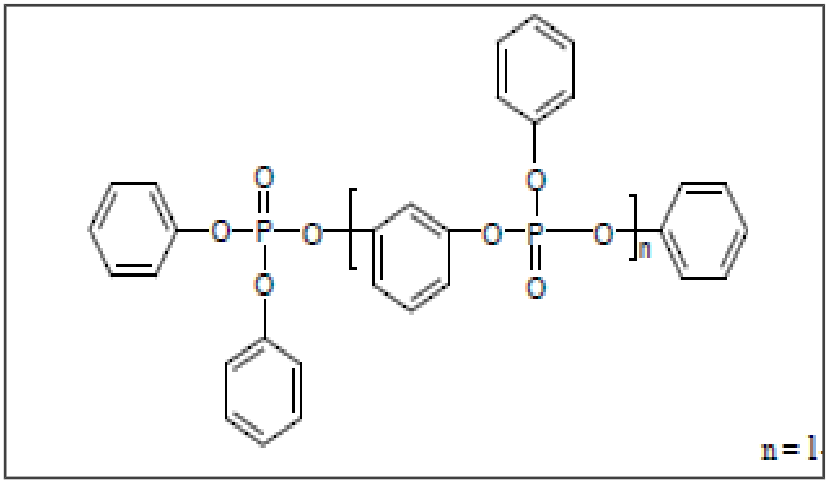
1.1 Other identifiers of the substance

Table 1: Other Substance identifiers

EC name (public):	Tetraphenyl m-phenylene bis (phosphate)
Physical strate	Liquid
IUPAC name (public):	Tetraphenyl 1,3-phenylene bis (phosphate) where n=1
CAS number:	57583-54-7
Index number in Annex VI of the CLP Regulation:	None
Molecular formula:	$C_{30}H_{24}O_8P_2$
Molecular weight or molecular weight range:	574.4543, where n=1
Synonyms:	Resorcinol bis-diphenylphosphate (RDP); Resorcinol bis (biphenylphosphate); Tetraphenyl resorcinol diphosphate;

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

Structural formula where n=1:



1.2 Other relevant information about substance composition

Table 2: Main constituents

Constituent	Typical concentration (w/w)	Concentration range (w/w)	Remarks
Tetraphenyl resorcinol diphosphate n= 1	72 %	> 60 % - < 75 %	n = 1 p = 2
Tetraphenyl resorcinol diphosphate n= 2	17 %	> 15 % - < 25 %	n = 2 p = 3
Tetraphenyl resorcinol diphosphate n= 3	4 %	> 3 % - < 6 %	n = 3 p = 4
Tetraphenyl resorcinol diphosphate n= 4	1 %	> 0.5 % - < 2 %	n = 4 p = 5
Tetraphenyl phosphate (TPP) **EC no: 204-112-2**	4 %	> 1 % - < 5 %	Another flame retardant

n = number of oligomers; p = number of phosphorus atoms

Table 3: Constituent: TPP

EC number:	204-112-2
EC name (public):	Triphenyl phosphate (TPP)
CAS number:	115-86-6
IUPAC name (public):	Triphenyl phosphate
Index number in Annex VI of the CLP Regulation:	None
Molecular formula:	C18H15O4P
Molecular weight or molecular weight range:	326,28

Structural formula

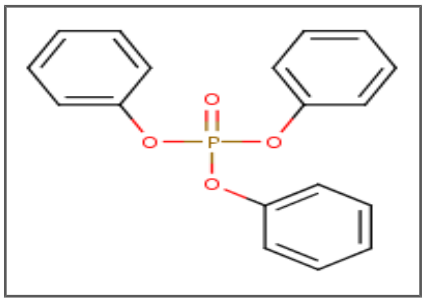
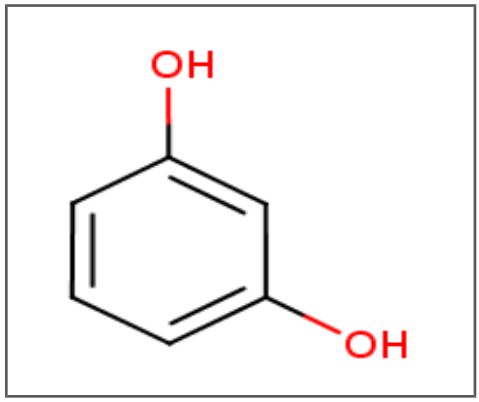


Table 4: Degradation (transformation) product or metabolite

EC number:	203-585-2
EC name (public):	Resorcinol
CAS number:	108-46-3
IUPAC name (public):	Resorcinol, Benzene-1,3-diol
Index number in Annex VI of the CLP Regulation:	604-010-00-1
Molecular formula:	C6H6O2
Molecular weight or molecular weight range:	110.11
Synonyms:	– 1,3-Benzenediol, *m*-Dihydroxybenzene – Resorcine

Structural formula:



2 OVERVIEW OF OTHER PROCESSES ON THE SUBSTANCE ITSELF/ EU LEGISLATION

Table 5: Completed or ongoing processes

RMOA	☐ Risk Management Option Analysis (RMOA) other than this RMOA	
REACH Processes	Evaluation	☐ Compliance check, Final decision
		☐ Testing proposal
		☒ CoRAP and Substance Evaluation The RDP is not on CoRAP but it should be noted that one of its constituent and one of its potential metabolite are on the CoRAP list: - Triphenyl phosphate (constituent) is on the CoRAP 2017 list by UK in particular for potential endocrine disrupting properties concern. - Resorcinol (potential metabolite of the parent compound) is on the CoRAP list 2016 by FI in particular for potential endocrine disrupting properties concern.
	Authorisation	☐ Candidate List
		☐ Annex XIV
	Restri-ction	☐ Annex XVII[1]
Harmonised C&L	☐ Annex VI (CLP) (see section 3.1)	
Processes under other EU legislation	☐ Plant Protection Products Regulation	
	☐ Biocidal Product Regulation	
	☐ Dangerous substances Directive	

1 Please specify the relevant entry.

revious	☐ Existing Substances Regulation
(UNEP) Stockholm convention	☐ Assessment
col)	☐ In relevant Annex
Other rocesses/ EU legislation	☐ Other (provide further details below)

No ongoing activity other than this RMOA.

It should be noted that one of its constituent and one of its potential metabolite are on the CoRAP list:

- Triphenyl phosphate (constituent) is listed on CoRAP 2017 by UK in particular for potential endocrine disrupting properties concern.

- Resorcinol (potential metabolite of the parent compound) is listed on CoRAP 2016 by FI in particular for potential endocrine disrupting properties concern.

3 HAZARD INFORMATION (INCLUDING CLASSIFICATION)

3.1 Classification

3.1.1 Harmonised Classification in Annex VI of the CLP

Table 6: Harmonised classification

Index No	International Chemical Identification	EC No	CAS No	Classification		Spec. Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard statement code(s)		
No current entry							

Self classification

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

Table 7: Self classification

Hazard class and category code(s)	Hazard statement code(s)	Number of notifiers
Not classified	/	60
Aquatic chronic 3	H412	61
Aquatic chronic 2	H411	17

- 17 notifiers indicated that an impurity or an additive present in the substance impacts the notified classification

3.1.2 Proposal for Harmonised Classification in Annex VI of the CLP

There is no current proposal for harmonised classification in Annex VI of the CLP.

3.1.3 CLP Notification Status

Table 8: CLP Notifications

	CLP Notifications[2]

2 C&L Inventory database, http://echa.europa.eu/web/guest/information-on-chemicals/cl-inventory-database (accessed 31 August 2016)

Number of aggregated notifications	7
Total number of notifiers	137

3.2 Additional hazard information

There is very little toxicity data for the RDP in all its forms (monomeric form: CAS N ° 57583-54-7 or polymeric forms). The few available data come almost exclusively from study reports of the chemical manufacture (US-EPA, 2015; CSR, 2015).

- Acute toxicity data by oral and inhalation routes where very low LD50 (LD50 > 5000 mg/kg orally; and LC50>4.14 mg/l by inhalation) were shown;
- In an acute exposure study[3] mono-esterase activity in males and females was reduced by 30 % on day 1 of treatment compared to before treatment (day -7) after exposure of rats by inhalation (4.14 mg/l for 4 hours),. After 14 days, mono-esterase activity returned to normal.
- Ocular irritation data with moderate and transient ocular irritation in rabbits;
- *In vitro* gene mutation and chromosomal aberrations (negative results);
- Mammalian erythrocyte micronucleus test in mice following single oral dose of 500 mg/kg bw (negative results);
- *In vivo* immunotoxicity study (see below);
- Two-generation study (see below)
- Toxicokinetic studies (see below).

The following data are not available:
- Skin and respiratory sensitisation study;
- Carcinogenicity study.

Almost all available toxicological studies concern the commercial RDP.
All available repeated dose toxicity studies are reported below.
It is not indicated in the studies whether the RDP is in monomeric or polymeric form.

3.2.1 Toxicokinetic of RDP

1. One *in vivo* toxicokinetic study (Freudenthal *et al*.; 2000) performed with **^{14}C RDP (99% purity)** to a single target dose of 100 mg/kg in 3 species (rats, mice and monkeys, 3 to 8 animals per sex and per route of exposure) and 4 routes of exposure (intravenous route: rats, mice and monkeys; gavage: rats, inhalation: rats, or dermal route: rats and monkeys) is available : The level of radioactivity was measured in plasma, faeces, urine, expired air, and in several tissues.

Results:

- RDP is rapidly and extensively absorbed by inhalation and oral route, and to a lesser extent by dermal route;
- RDP is extensively metabolized. Metabolism was consistent between species, sexes, and individual animals
- Metabolites were found in significant concentrations only in the feces of animals exposed by inhalation or by oral route. No significant difference was observed in the "metabolic profiles" between species and sexes and according to the route of exposure.

3 https://echa.europa.eu/registration-dossier/-/registered-dossier/15877/7/6/5

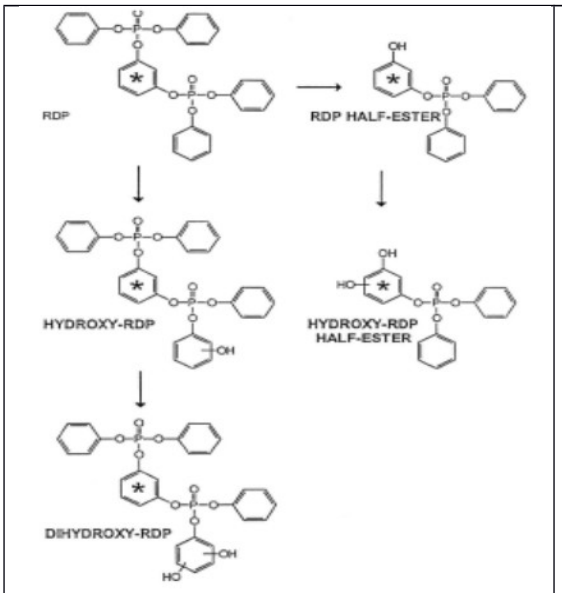
- The authors indicate that Cmax in rats after inhalation, oral, and dermal exposures were 42%, 10%, and 1% respectively.
- Inhalatory absorption of 60% and an oral absorption of 58% (based on the AUC compared with IV) were determined in rats.
- After dermal exposure in the rat the dermal absorption was estimated to be 15% (based on the AUC compared with IV). The monkey study reported a lower or no dermal absorption (<9%). However based on the low recovery (67%), this value appears less convincing.
- Distribution of RDP was studied after intravenous injection in the rat (IV dose of 100mg/kg). RDP was mainly distributed to the lungs (5-10%). Tissues other than lungs demonstrated comparable levels of radioactivity, with liver and fat showing slightly more radioactivity than other tissues and carcass, and the brain showing less radioactivity.
- All IV studies (mouse, rat, and monkey) show that the primary route of elimination is the faeces (ca 50%) and secondary the urine. A minimum is excreted *via* expired air.
- In the rat after IV-, oral- and inhalatory exposure a half-life of 2,5 days was reported. After dermal exposure the half-life was slightly higher (3,7 days).
- Excretion rate (radioactivity) is predominantly in the feces and in the urine, and slightly in the exhaled air (for all routes);

According to the authors of the study, the lungs act as "transient storage depot" following intravenous exposure and to a lesser extent from exposure by inhalation and oral route. Radiographic examinations have shown that radioactivity is concentrated in the pulmonary vascular tissue (not in the alveolar epithelium), before declining gradually. This is due to the hydrophobic nature of the RDP.

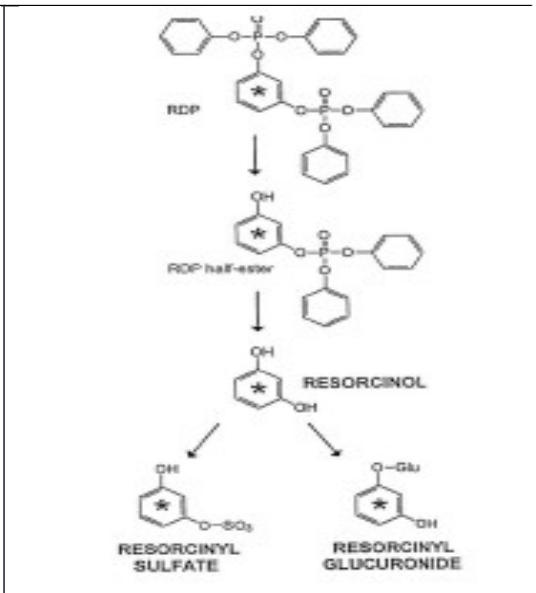
Identification (but no quantitative data) of major metabolites:

- Major fecal metabolites: resorcinol diphenylphosphate (RDP half ester), hydroxy-RDP half ester, dihydroxy-RDP, and hydroxy-RDP.
- Major urinary metabolites: resorcinol, resorcinyl glucuronide, and resorcinyl sulfate.

Figure 1: Metabolic pathway of RDP. *In vivo* data



The metabolic pathway of RDP to form



The metabolic pathway of RDP to

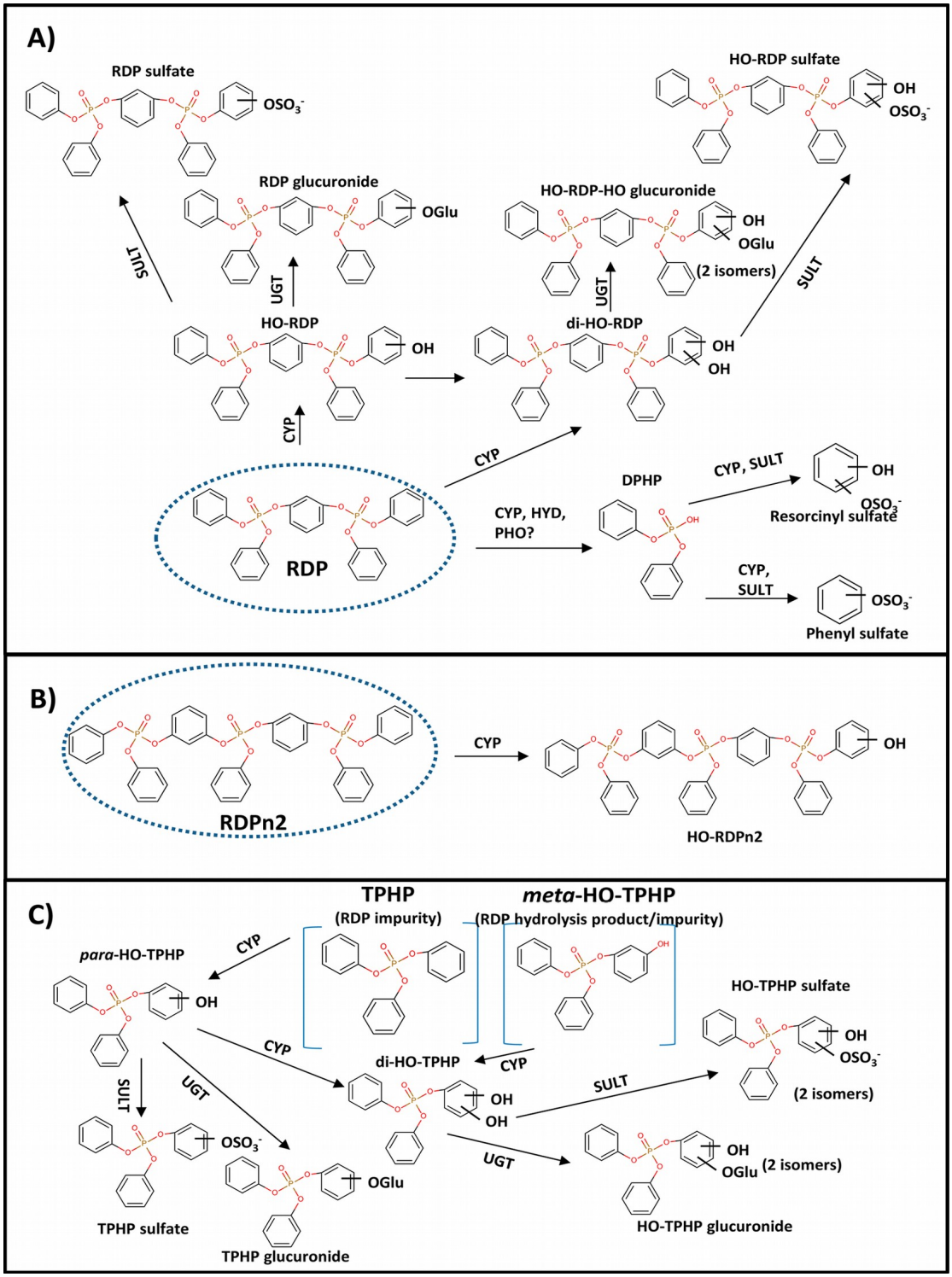
the four major metabolites isolated and identified from **the feces** of rats, mice, and primates.	form the three major metabolites isolated and identified **from the urine** of rats, mice, and primates.

2. In another recent *in vitro* study from Ballesteros-Gómez et al., (2015), the metabolism of **RDP (98% purity)** and its oligomers was investigated using human liver microsomes and human liver cytosol. Mono- and dihydroxy-metabolites, together with glucuronidated and sulfated metabolites, were also detected when Hydroxyl metabolites were incubated with either microsomes in the presence of uridine 5'-diphosphoglucuronic acid (UDPGA) or cytosols in the presence of adenosine 3'-phosphate 5'-phosphosulfate (PAPS), respectively. Regarding RDP oligomers, only a hydroxymetabolite of the dimer could be detected. RDP and its oligomers were also readily hydrolyzed, giving rise to a variety of compounds, such as diphenyl phosphate, para-hydroxy-triphenylphosphate, and para-hydroxy RDP, which were further metabolized.

3. Another more recent study (Van den Eede et al., 2016) shows that when triphenylphosphate (TPP) was 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*.

Figure 2: Metabolic pathway of RDP in its monomeric or dimeric forms and of TPP and meta-HO-THP. In vitro data.

It should be noted that "TPHP" is also designated by "TPP". That is the case in this report.



Legend: Metabolites of (A) RDP and of (B) RDPn2 (dimer) identified in this study. Those derived from TPHP (RDP impurity) and meta-HO-TPHP (RDP hydrolysis product/impurity) are also shown in (C), since they are present in RDP solutions. (Abbreviations: HYD, chemical hydrolysis; PHO, phosphatases, possible pathway but not confirmed).

4. Summary and discussion of toxicokinetic of RDP

The data on toxicokinetic of RDP indicate that, in rats, this compound is well absorbed by inhalation and by oral route, whereas absorption occurs at limited extent *via* dermal exposure. Comparative studies carried out in mice, rats and cynomolgus monkey with radiolabelled RDP showed that this compound was extensively metabolized in these species (Freudenthal *and al.*, 2000). Mono- and di-hydroxylated triphenylphosphate, as well as resorcinol, and corresponding sulfate and glucuronide conjugates, were identified in feces and urine of exposed animals by inhalation and oral routes. There is no quantitative data of metabolites of RDP. No trace of free triphenylphosphate (TPP) *in vivo*.

Biotransformation of RDP was investigated also using human liver subcellular fractions. Mono- and di-hydroxylated RDP as well as mono- and di-hydroxylated triphenylphosphate were identified in microsomes incubated with RDP and appropriate co-factors. Corresponding glucuronidated and sulfated metabolites were also detected (but no quantitative data). When triphenylphosphate (TPP) was incubated with primary human hepatocytes, diphenylphosphate and monohydroxylated triphenylphosphate were the major metabolites formed, but no trace of resorcinol was detected.

To sum up, these data indicate that the production of resorcinol from RDP is possible, but due to the efficiency of phase II metabolic pathways (conjugation), the presence of resorcinol in target tissues should be limited, if any. The data on resorcinol will therefore not be included in the upfront evaluation.

3.2.2 Repeated toxicity studies of RDP

1. In a 4-week inhalation study (Henrich et al., 2000), Sprague-Dawley rats (10/sex/group) were exposed (aerosol, nose only) to 0, 100, 500 or 2,000 mg/m^3 (0, 0.1, 0.5, or 2 mg/L) **commercial RDP** (named Fyrolflex RDP). Ten rats/sex/group were euthanized on day 29; 10 additional rats/sex in the control and high-dose groups were euthanized after a 60-day recovery period. According to the authors, a complete necropsy was conducted on each study animal from all dose groups at the end of the 28-day treatment period and a histological examination of the following tissues was performed: adrenal glands, brain, buccal mucosa, epididymides, esophagus, heart, kidney, larynx, liver, lungs, nasal cones, ovaries, pancreas, pituitary gland, vertebral column, spleen, testis, thymus, thyroid gland (with parathyroid) and trachea. At the recovery necropsy, only the lungs were weighed.

Plasma cholinesterase and erythrocyte cholinesterase was measured for all dose groups on day 7 and day 29, and only for the control and high exposed groups on day 89 (recovery).

Monocyte nonspecific esterase (MNSE) activity was measured for all dose groups on days 29 (post exposure), and only for the control and high exposed groups on days 61 and 89 (recovery).

Results:

- No deaths or clinical signs of toxicity were observed. Body weight and body weight gain were reduced in high-dose male rats during exposure, but returned to control levels after 5 weeks of recovery. Relative liver weights were increased after exposure in mid- and high-dose females and in high-dose

males. A dose-related increase in absolute and relative lung weights was seen in the test group, and was significant in mid- and high-dose animals. This persisted in high-dose animals during recovery. White foci in the lungs were observed at 2,000 mg/m^3 and alveolar histiocytosis at 500 and 2,000 mg/m^3.

- According to the authors "no exposure-related gross or microscopic pathology was identified in any other organ in any experimental group". They give no further indication on the results related to weight and histopathology of organs examined.

- Mean plasma cholinesterase activity levels were significantly decreased in high-dose males (15% inhibition) and mid- and high-dose females (38% and 64% inhibition, respectively) compared to the respective control group at the end of the 28-day exposure period; a significant decrease (15% inhibition) was still present in the high-dose females at the end of the recovery period. No effects on erythrocyte cholinesterase activity levels were seen.

- Monocyte nonspecific esterase (MNSE) activity[4] levels were increased in low- and mid-dose rats (respectively + 44 % and + 76 % compared to controls) at the end of the 28-day exposure period. MNSE activity levels in the high-dose animals were similar to control values after the exposure period and during and at the end of the recovery period. Values of MNSE are for both sexes.

The detailed results of plasma cholinesterase and MNSE activity are summarized in the following tables (Henrich et al., 2000).

4 Occupational exposure to organophosphates leads to changes in the activity of the three enzymes: plasma cholinesterase, erythrocyte cholinesterase, and MNSE (See the following study)

TABLE 2

Mean cholinesterase activity levels (IU/l) in male and female rats exposed by nose-only inhalation to aerosols of RDP 5 days per week for 28 days, followed by 60 days of recovery

	Plasma cholinesterase (mean ± SD)			Erythrocyte cholinesterase (mean ± SD)		
Exposure group	Day − 7[a]	Day 29[b]	Day 89[c]	Day − 7[a]	Day 29[b]	Day 89[c]
			Males			
Filtered air control	537 ± 84	395 ± 40	424 ± 122	8459 ± 442	9019 ± 324	7925 ± 655
0.1 mg/l RDP	588 ± 83	437 ± 78	—[d]	8780 ± 640	8956 ± 214	—
0.5 mg/l RDP	596 ± 96	383 ± 57	—	8112 ± 387	8900 ± 318	—
2.0 mg/l RDP	578 ± 80	334 ± 27*	375 ± 78	7905 ± 515	8761 ± 255	8031 ± 582
			Females			
Filtered air control	1278 ± 265	1523 ± 386	2502 ± 326	7721 ± 526	8920 ± 339	8264 ± 591
0.1 mg/l RDP	1045 ± 148	1636 ± 296	—	7383 ± 829	8973 ± 245	—
0.5 mg/l RDP	949 ± 116	951 ± 171*	—	7340 ± 478	8862 ± 297	—
2.0 mg/l RDP	1087 ± 255	551 ± 111*	2119 ± 405*	7345 ± 461	8701 ± 561	8128 ± 918

[a]Pre-exposure; $N = 20$ in the control and high-dose groups, $N = 10$ in the low- and mid-dose groups.
[b]Postexposure; $N = 9$ to 10.
[c]Recovery; $N = 8$ to 10.
[d]— = not measured; all rats in the low- and mid-dose groups were sacrificed on day 29.
*Significantly different from control, $p \leq .05$.

TABLE 3

Mean monocyte nonspecific esterase activity levels of male and female rats exposed by nose-only inhalation to aerosols of RDP 5 days per week for 28 days, followed by 60 days of recovery

Exposure group	Mean monocyte nonspecific esterase activity (% filtered air control activity level)			
	Day — 7[a]	Day 29[b]	Day 61[c]	Day 89[d]
Filtered air control				
Mean	100.00	100.00	100.00	100.00
SD	28.91	47.82	20.52	16.57
N	102	36	18	12
0.1 mg/l RDP				
Mean		143.87	—[e]	—
SD		46.37		
N		12		
0.5 mg/l RDP				
Mean		176.28	—	—
SD		16.48		
N		9		
2.0 mg/l RDP				
Mean		108.21	98.66	109.78
SD		43.40	14.46	16.66
N		34	18	14

[a]Pre-exposure.
[b]Following the 28-day exposure period.
[c]Following 33 days of recovery.
[d]Following 60 days of recovery.
[e]— = not measured; all rats in the low- and mid-dose groups were sacrificed on day 29.

2. Based on the knowledge that occupational organophosphorus exposure leads to changes in circulating monocytes as a result of inhibition of surface monocyte esterase (Levine et al., 1986), associated with a mild decrease in erythrocyte

acetylcholinesterase but no change in plasma pseudocholinesterase or lymphocyte neurotoxic esterase, Sherwood et al., (2000) designed a study to determine the possible immunosuppressive properties of **commercial RDP** (named Fyrolflex RDP). The authors indicated that the study is part of a safety assessment program undertaken by the manufacturer to check the product's toxicity. They add that the test battery of immune function assays was selected from those recommended by the National Toxicology Program (NTP) for immunotoxicity evaluation of xenobiotics. Female $B_6C_3F_1$ mice (50/group) were exposed *via* oral gavage (for 28 days and following a 60-day recovery) to 0, 500, 1,500, or 5,000 mg/kg/day RDP (resorcinol bis-diphenylphosphate). The results are:

- No deaths, clinical signs of toxicity or effects on body weight or examined organ (thymus and spleen) weights.
- No adverse histopathological changes or necropsy findings (thymus, spleen, representative mesenteric, mandibular and mediastinal lymph nodes, and all gross lesions). Effects on thyroid or on adrenal glands have not been investigated.
- No treatment-related changes in peritoneal cell numbers or cell types, peritoneal macrophage phagocytic activity or host susceptibility to infection.
- No adverse effect on splenic natural killer cell activity, lymphocyte blastogenesis, or antibody-forming cell function.
- The activity of Plasma Pseudocholinesterase (PPCHE) and Red Cell Cholinesterase (RBCCHE) was tested prior to dose initiation, on day 29 after 28 days of dosing, and after a 60-day recovery period. Pretest PPCHE activity was significantly lower than that of the controls after both 28 days of dosing and 60 days of recovery. Pretest RBCCHE activity was significantly higher than that of the sham controls at the day 29 time point.
- According to the authors, differences between baseline and -control values may have been due to the comparison against separate naïve animals for baseline values, rather than against pretest sera from the sham-control animals.

Conclusion:

Significant decrease in erythrocyte cholinesterase activity and in plasma pseudocholinesterase activity in all groups of exposure, but both enzyme activities returned to control levels at the end of 60 day recovery period. No other adverse effect was seen.

The detailed results are summarized in the following table (Sherwood et al., 2000):

TABLE 2

Effect of oral gavage exposure to Fyrolflex RDP on mouse plasma pseudocholinesterase and red cell cholinesterase levels after 28 days of exposure and after 60 days recovery[a]

Exposure group	Dose (mg/kg/day)	Test day		Plasma pseudocholinesterase (IU/l)	Red cell cholinesterase (IU/l)
Predose (baseline)	0	0	Mean	6858*	7702*
			SEM	232.4	299.9
Sham control	0	29	Mean	8578†	6516†
			SEM	324.2	169.8
High RDP[b]	5000	29	Mean	1534*†	6537†
			SEM	56.8	118.6
Mid RDP	1500	29	Mean	2276*†	6314†
			SEM	157.9	143.0
Low RDP	500	29	Mean	3374*†	6436†
			SEM	160.5	117.3
Sham control	0	88	Mean	10278†	7904
			SEM	232.4	93.4
High RDP	5000	88	Mean	9877†	8430†
			SEM	327.9	146.3
Mid RDP	1500	88	Mean	9852†	8277
			SEM	242.2	124.7
Low RDP[b]	500	88	Mean	9770†	8116
			SEM	282.8	169.1

[a] $N = 10$ unless otherwise indicated.
[b] $N = 9$.
* Significantly different from sham control, $p \leq .05$.
† Significantly different from predose (baseline), $p \leq .05$.

3. In a short-term repeated dose toxicity study published on the Echa site[5], a **commercial RDP** (named CR733S) was administered by IP injection to males and females rats Sprague Dawley (at 0, 0.000175, 0.00175, 0.5, 50 or 500 mg/kg bw/day) for 28 days. 50 mg/kg bw/day Triphenyl phosphate (TPP) was used as comparative control. Animals were observed twice daily for signs of toxicity or mortality. Body weight and food consumption were assessed. Urine and blood samples were collected for evaluation of hematology, clinical chemistry and cholinesterase activity prior to necropsy.

Results:

- No mortality and adverse clinical signs were observed in any group. No effect on body weight, food consumption, whole blood or erythrocyte cholinesterase, hematology or serum chemistry parameters or urinalysis (no other precision);
- Significant increase in relative liver weight for both sexes in the 500 mg/kg bw/day group, and in the TPP control group;
- No information on the weight or histological examination of any organ.
- Local irritation of mesentery and adjacent adipose tissue or on the serosal surface of some visceral organs in 500 mg/kg bw/day group;
- Slight to moderate fat necrosis and granulomatous inflammatory response, increased number of lymphoid cells and macrophages, and presence of numerous multinucleated phagocytic giant cells in the 500 mg/kg bw/day group.
- Significant decrease in plasma cholinesterase for both sexes of 500 mg/kg bw/day group, and for females of 50 mg/kg bw/day, and for TPP control group;
- Clear inhibition of plasma cholinesterase activity for both sexes in the 50 and 500 mg/kg bw/day groups and in TPP control group.
- No quantitative data and no other precision;

5 https://echa.europa.eu/registration-dossier/-/registered-dossier/15877/7/6/5

- NOAEL = 0.5 mg/kg bw/day.

4. In another short-term repeated dose toxicity study published on the Echa site[3], female mature hens (White Leghorn) were exposed by oral gavage to **commercial RDP** (named Fyrolflex RDP) at 2,000 mg/kg bw/day for 5 days and a recovery period of 14 days. Positive (60 mg/kg bw/day tri-ortho-cresyl phosphate; ToCP[6] in corn oil) and negative (corn oil) control were also included. Examinations performed were morbidity and mortality, body weight and histopathology. The Neuropathy Esterase Activity was evaluated in a Neuropathy Target Esterase (NTE) assay.
No deaths were observed and no overt signs of toxicity were detected in any of the animals. Additionally, no overt differences were detected in the body weights or body weight changes of RDP treated hens as compared to positive or negative control. No information on the weight or histological examination of any organ. Weight loss in all groups was similar during study. NTE activity was completely (100%) inhibited in positive control hens (as expected), and slightly (14%) inhibited in treated hens. This result shows that the RDP induces a slight delayed neurotoxicity.

3.2.3 **Developmental toxicity studies of RDP**

1. In a developmental oral gavage study (Ryan and al, 2000), Pregnant New Zealand white rabbits (27/group) were dosed with 0, 50, 200 or 1,000 mg/kg/day **RDP (not commercial- purity not specified**) by oral gavage from GD6 to GD28, and sacrificed on GD29. Histopathological examinations were limited to the liver, kidneys, and spleen.
No clinical signs of maternal toxicity were evident during the study or were apparent from gross necropsy observations. According to the authors, no significant differences were observed between the test substance-treated groups and the vehicle control groups for:
- Mean body weights, body weight gains, food consumption,
- Uterus, liver, kidney, and spleen weights;
- Fetal deaths, resorptions, or malformations;

However, it should be noticed that cephalic malformations were observed in 3 fetuses from 2 different litters at the highest dose and several malformations including retinal anomalies were observed in one fetus.

The authors stated the NOAEL at 1,000 mg/kg for maternal and developmental toxicity. However, depending on the observed malformations, the NOAEL should be fixed at 200 mg/kg for fetal toxicity.
2. In a two generation oral study (Henrich et al, 2000), Sprague-Dawley rats (30/sex/dose) were fed with 0, 50, 500, or 1000 mg/kg/day (0, 1 000, 10 000, or 20 000 ppm) **commercial** RDP (named Fyrolflex) in the diet. Parent animals (P1) were treated for 10 weeks prior to mating, during the 2-week mating period, through-out gestation, and through lactation until sacrifice. The F1 generation was treated following a regimen similar to P1. All F2 pups and F1 sires and dams were sacrificed after weaning. The F2 generation was not intentionally exposed to the test diet. According to the authors, only the following tissues (from 20 randomly selected P1 rats per group in the control and high-dose groups) were processed and examined microscopically: vagina, uterus, ovaries with oviducts, cervix, testes, epididymides, prostate, and seminal vesicles (not thyroid, thymus, and adrenal glands). They indicated that only ovaries, testes and gross lesions

6 ToCP: isomer of TCP. Considered to be the most neurotoxic triester phosphate, and known to cause delayed neurotoxicity (NR) (characterized by ataxia and limb weakness) and appearing 10 to 14 days after exposure.

from 20 F1 animals per group (selected for mating in the control group and high dose groups) were examined, and that the livers from 10 males and 10 females (from the control and high dose groups) in each of the P1 and F1 generations were also evaluated microscoscopically.

Results:

-For parents (P1): No clinical signs of toxicity. No effects on litter survival. No adverse effects on any reproductive or fertility parameter measured. No treatment-related histopathological lesion in any reproductive organ was observed at 1000 mg/kg bw/day. However, an increase in weight of the adrenal glands which is significant for males P1 at medium and high doses and for females P1 at all doses.

-For F1: There were no significant differences between the control groups and treatment groups for the following reproductive parameters: number of breeding pairs, number sperm positive, percent mated, number selected for littering, percent successful parturition, total born day 0, and live days: 0, 7 21. There is a significant increase in the weight of the adrenal glands (at high dose in males, and at medium and high dose in females) without change at low dose. Mean anogenital distance measured at birth (postnatal day 0) was similar in the control and high-dose groups (control males 4.9 ± 0.6 vs. high males 5.1 ± 0.5; control females 2.8 ± 0.4 vs. high females 2.7 ± 0.4 mm), but it was measured only in one pup per sex per litter.
-A delay of ~ 3 to 5 days was observed for preputial separation and vaginal opening at 500 and 1000 mg/kg/day bw respectively (Observations at PND 34-55 for males, and at 28-45 for females). Those delays were statistically significant.
-NOAEL: 50 mg/kg bw-day (for delay of vaginal opening and preputial separation) LOAEL: 500 mg/kg bw-day.
-Nipple retention was not measured.
-The table below summarizes the values of food consumption and age at developmental landmarks.

Summary of F_1 week 1 food consumption (g/week), body weight (g), and age at developmental landmarks (days)

		Study group			
			RDP dose		
		Control	1000 ppm	10,000 ppm	20,000 ppm
Males					
Food consumption[a]	Mean	167	167	167	156
	SD[b]	36.0	31.8	38.7	34.3
	N	24	25	28	26
Initial body weight[c]	Mean	101	97	85*	74*
	SD	8.4	11.7	11.0	8.1
	N	25	25	28	26
Preputial separation	Mean	37.1	38.2	40.6*	42.2*
	SD	2.54	3.23	4.82	5.27
	N	25	25	28	26
Final body weight[d]	Mean	515	470*	459*	446*
	SD	52.1	35.5	42.9	53.0
	N	25	25	28	26
Females					
Food consumption[a]	Mean	140	141	118*	110*
	SD	40.1	33.5	23.0	15.3
	N	25	25	28	26
Initial body weight[c]	Mean	92	90	78*	70*
	SD	7.1	8.9	8.3	8.2
	N	25	25	28	26
Vaginal patency	Mean	32.0	32.9	34.9*	36.8*
	SD	2.03	2.02	2.42	3.16
	N	25	25	28	26
Final body weight[e]	Mean	319	302*	300*	293*
	SD	29.7	22.7	23.4	23.6
	N	25	25	27	25

*Significantly different from control, $p \leq .05$.
[a]Week 1.
[b]*SD* = standard deviation.
[c]Week 0 (postweaning; 26–29 days of age).
[d]Week 16 (postmating).

For F2: At birth, postnatal day 0 body weights of the test substance treated groups were comparable to controls. However, by postnatal day 4, body weights of the F2 low-, mid- and high-dose pups were significantly decreased compared to control pups, which persisted until postnatal day 21. According to the authors, the body weight decreases on postnatal days 4 and 7 were considered in part to be associated with litter size effects (they do not specify which effects), whereas the latter decreases in body weight for the low-, mid-, and high-dose groups were considered to be related with the taste aversion phenomenon.
No other clinical signs of toxicity, no effects on litter survival, and no treatment-related histopathological lesions.

Table 9 Summary of effects of RDP

Repeated toxicity studies		**References**
Rats Sprague Dawley males and females Inhalation (nose-only) 28 days: 0.1, 0.5, 2 mg/L Recovery period = 60 days	- Significant decreased mean plasma cholinesterase activity at the end of exposure in 2000 mg/m^3 males group (15% inhibition) and in 500 and 2000 mg/m^3 females group; - Significant decrease is still present at the end of recovery period ; - Increased MNSE activity at the end of exposure in 100 and 500 mg/m^3 group (15% inhibition);	Henrich *and al.* (2000)

Repeated toxicity studies		References
Commercial RDP (named Fyrolflex RDP).	- MNSE activity is similar to control during and at the end of recovery period.	
Female mice B6C3F1 Oral gavage 28 days, with 60-day recovery 500, 1500, 5000 mg/kg/day Recovery period = 60 days Commercial RDP (named Fyrolflex RDP)	-Decreased erythrocyte cholinesterase activity and plasma pseudocholinesterase activity in all groups of exposure; - Values of enzyme activity returned to control levels at the end of recovery period.	Sherwood *and al.* (2000)
Rats Sprague Dawley males and females IP injection 28 days: 0, 0.000175, 0.00175, 0.5, 50, or 500 mg/kg bw/day Triphenyl phosphate (TPP) = positive control (50 mg/kg bw/day) Commercial RDP (named CR733S)	- Increased number of lymphoid cells and macrophages and presence of numerous multinucleated phagocytic giant cells in the 500 mg/kg bw/day group; - Significant decreased plasma cholinesterase activity (no precision) for both sexes of 500 mg/kg bw/day group, and for females of 50 mg/kg bw/day, and for TPP control group; - Clear inhibition of esterase activity (no precision) in the 50 and 500 mg/kg bw/day groups and in TPP control group; NOAEL = 0.5 mg/kg bw/day. - No effect on the thymus	Report not published and resumed on Echa site (Year of study: 1989)
Female hens (White Leghorn) Oral gavage 5 days: 2000 mg/kg/bw/day	- Slight inhibition of NTE activity (14%) in treated hens. - Total inhibition of NTE activity (100%) in positive control hens;	Report not published and resumed on Echa

Repeated toxicity studies		**References**
Positive control = ToCP (60 mg/kg bw/day) Negative control (corn oil) Commercial RDP (named Fyrolflex RDP)		site (Year of study: 1994)
Developmental toxicity studies		References
Pregnant rabbits Oral gavage Gestation days: 6 to 28; 50, 200, 1000 mg/kg/day RDP (purity not specified)	-Cephalic malformations in 3 fetuses of 2 different litters at 1000 mg/kg/day, not observed at 50 and 200 mg/kg/day. -No other significant differences between the treated groups and the control group. NOAEL = 200 mg/kg kw/day for fetal toxicity.	Ryan *and al.* (2000)
Two generation oral study Sprague-Dawley rats 50, 500, or 1000 mg/kg/day Parent animals (P1) and F1 generation treated with a similar regimen F2 generation not treated Commercial RDP (named Fyrolflex).	-P1: increase in weight of the adrenal glands; -F1: Significant increase of adrenal glands weight, and delay (3 – 5 days) in preputial separation and vaginal opening at the two highest doses; - Nipple retention not measured; - No effect on anogenital distance at all dose levels; F2: Significant decrease of body weights between PND 4 and PND 21. NOAEL(P1): = 1000 mg/kg bw/day NOAEL (F1): 50 mg/kg bw/day	Henrich *and al.* (2000)

3.2.4 Summary and discussion of toxicity of RDP

Of the 5 available repeated toxicity studies performed with commercial RDP, which can contain up to 5% TPP.

The neurotoxicity of RDP was investigated in three toxicity studies in rodents, *via* inhalation, oral, or IP routes. Plasma and erythrocyte cholinesterase activity, and plasma pseudocholinesterase activity were assessed. Monocyte non-Specific Esterase (MNSE) activity was measured as an additional parameter.

The results of these studies show a significant decrease in plasma cholinesterase activity and in erythrocyte cholinesterase activity, no significant changes in MNSE activity without any adverse histopathological changes or weight changes in thymus, and spleen following 4-week oral or inhalation exposure nor histopathological changes in thyroid organ following 4-week inhalation exposure.
By IP route on rats SD, RDP causes a significant decrease in plasma cholinesterase activity, an increased number of lymphoid cells and macrophages, and a presence of numerous multinucleated phagocytic giant cells.

After exposure of hens during 5 days (oral gavage, 2000 mg/kg/bw/day), RDP causes a 14% decrease of the enzyme neuropathy target esterase activity, compared to positive controls (which have been exposed to ToCP at 60 mg/kg bw/day).

The results of these three studies support the a potencial neurotoxicity of RDP. However, additional data are needed to rule on a possible neurotoxic effect of RDP in humans.

In a developmental toxicity study performed with non-commercial RDP (purity level not specified, nor the proportion of monomer or oligomer), exposure of pregnant rabbits to RDP by oral gavage (from gestation day 6 through 29) up to 200 mg/kg bw/day was found not to result in maternal and developmental toxicity in rats. At 1000 mg/kg bw, cephalic malformations were observed in 3 fetuses of 2 different litters.

In a two-generation reproduction toxicity study, male and female rats (P1 and F1) were exposed to commercial RDP in the diet for approximately 11 weeks prior to mating, during and up to 2 -3 weeks of mating and until sacrifice (males) or during gestation up to the weaning of the pups (females). Mortality, clinical signs, body weights, food consumption and organ weights were recorded, reproductive function was assessed and gross necropsy and histopathology were performed.

For parents P1, the main effect is an increase in weight of the adrenal glands, which is significant for males at medium and high doses and for females at all doses.

For F1, there is a significant increase in the weight of the adrenal glands, and a significant delay in preputial separation and vaginal opening at the two highest dose levels. According to the authors, this latter effect is attributed to the decreased preweaning food consumption and corresponding reduced body weight caused by flavour aversion to the test substance in the food. This reduction in pup body weight beginning on postnatal day 14 was attributed to lower maternal/litter food consumption noted during lactation. However, treated animals had decreased body weights compared to controls during week 1 at 500 and 1000 mg/kg bw/day, and also during week 16 at 50, 500, and 1000 mg/kg/day. Thus, after weaning and an adjustment period, food consumption increases and it is not different compared to controls. There are not as many compensation of weight retardation, and there hold delay pubertal process in both sexes, but in general, growth retardation is compensated after a recovery in consumption food after weaning. Based on these data, it is difficult to state whether this effect is

secondary to the decline in weight following the decline in food consumption, or whether it is the consequence of a direct effect of the RDP.
In summary, the results of these latter studies have not excluded a possible effect of RDP on embryonic development, but more data is needed to make a final assessment.
The effects of RDP on the thyroid and the thymus (together) and on the thymus (alone) were only investigated by two studies among the six identified (oral and inhalation routes for 28 days) and in only one study (inhalation route for 28 days) respectively. No effect on weight and structure of these two glands were reported.

3.2.5 Toxicity of Resorcinol and of TPP

Pharmacokinetic and metabolic data indicate that RDP is metabolized in vivo mainly in hydroxylated triphenylphosphate (HO-TPP) and resorcinol (IPCS-CICAD, 2006). In this context, the potential thyroid disrupting properties of those two compounds was examined.

Summary of toxicity data of resorcinol
The toxicokinetic and metabolism of resorcinol has been reviewed by Lynch et al. (2002). This compound is rapidly absorbed and eliminated in the form of glucuronide and sulfate conjugates, suggesting low bioavailability of resorcinol.
In vivo data are summarized in the "concise international chemical assessment" report on resorcinol (IPCS-CICAD, 2006). The authors indicate that there are some discrepancies between studies regarding the potential deleterious effect of resorcinol on the thyroid function (Welsch F., 2008).

The earliest publications underlines the fact that the effect (in particular on the primary mechanisms of action i.e. inhibition of thyroid iodine uptake) are very short-term (Arnott and Doniach, 1952). These effects can last longer when resorcinol is administered as a diacetate as a prodrug (Doniach and Logothetopoulos, 1953) insuring a prolonged release and more continuous exposure such as the one obtained with repeated administration of resorcinol in oil solutions.

The effect on the thyroid gland histology and structure is characterized by a hyperplasia, that is observed only with long lasting continuous exposure. In rodents, this hyperplasia might be due to a relative hypothyroidism following a decrease in iodine uptake and/or TPO (thyroid peroxidase, the rate limiting enzyme of thyroid hormone biosynthesis) activity. The effect of resorcinol on the thyroid function appeared to be reversible. Thus, differences in the evaluated parameters and the timing of this evaluation relative to the treatment period can explain, at least in part, the discrepancies between the studies.

Interestingly, none of the study performed through gavage evidenced an effect of resorcinol on the thyroid function. This might be explained by a very efficient hepatic first pass effect with this route of administration, leading to an extremely low bioavailability of the compound. Interestingly diet or drinking water administration can partly escape this effect, whenever absorption can occur at the level of the mouth epithelium as for most of small lipophilic molecules and, the subcutaneous route is not at all associated to hepatic first pass effect.

The only convincing human data linking resorcinol exposure to thyroid disruption arise from clinical case reports from patient submitted to long term skin application of large amount of resorcinol ointment on a debilitated skin (for

review see Lynch et al., 2002). This is fully consistent with the fact that in animal data long term, high dose parenteral exposure are the most efficient to induce a thyroid disruption.

Although resorcinol might present some thyroid disrupting properties resulting from its ability to interfere with thyroid iodine uptake and thyroid hormone biosynthesis demonstrated both in vitro and in vivo, these effects to be expressed require continuous long term exposure at relatively high dosage regimen and a consequent accumulation within the thyroid gland itself since TPO, the targeted enzyme, is strictly intracellular.
Given the pharmacokinetic properties of resorcinol and in particular its very high clearance rate and intensive hepatic metabolism for it to mediate the thyroid disrupting effect of RDP would require a very high and prolonged metabolisation rate of RDP into resorcinol which does not seem to be the case.

Therefore, in the current stage of knowledge, it seems very unlikely that resorcinol, as a metabolite of RDP, might mediate effect on the thyroid function.

Summary of toxicity data of TPP

Human data

- Substance found in breast milk (ATSDR, 2012)
- Observation of an association between a decrease in sperm count and impairment of the level of hormones (related to fertility and thyroid function), with a high level of TPP in indoor dusts. The specific effect of the TPP is not known (Meeker and Stapleton, 2010)

Other data

The main metabolic pathway of triphenylphosphate is hydroxylation to mono- and di-hydroxylated triphenylphosphate and diphenylphosphate (See above in 3.2.1).

Data regarding TPP and its hydroxylated metabolite on thyroid homeostasis are scarce and limited to in vitro data and/or animal model on the edge of in vivo (zebrafish embryos).

TPP showed neither agonist nor antagonist properties in either dual-luciferase gene reporter assay for thyroid receptor β (TRβ) or GH3 cell proliferating test (Zhang et al, 2016).

TPP (2 mg/L in water) caused transcriptional responses also found in TRα-centered gene network in zebrafish embryo larvae while at this concentration it did not affect hatching or survival rates (Liu et al. 2013).

Consistently, reporter gene assay for the screening of TRα/β agonist and antagonist activities in CHO-K1 transfected cells did not evidence either TR agonist or antagonist activities of TPP (Kojima et al., 2013). In the GH3 cells, a pituitary cell line with a TH-dependent proliferation, TPP at 100ng/ml increases the expression of several genes related to thyroid regulation: TSHβ, TRα, TRβ and deiodinase 1. In the thyroid cell line FRTL5, TPP can modify the expression of key genes of TH biosynthesis. In particular, it increases the sodium/iodide symporter (NIS) gene expression at 3 and 10 µg/ml and TPO at 10 µg/ml.

TPP increases T4 and T3 whole body concentrations for concentration as low as 40ng/ml in water in zebrafish along with a modulation of the expression of several TH-regulated genes and or genes involved in the regulation of the thyroid axis embryo (Kim et al., 2015). Except for the effect on the TH-binding protein, transthyretin (TTR), those effects on gene expression require higher concentrations than the effect on T4 and T3 concentrations.

Although both the meta and para hydroxylated metabolites of TPP exhibited some estrogenic and glucocorticoid properties in a dual-luciferase gene reporter assay, they did not show any TRα agonist or antagonist activities for concentrations ranging from 0.1 µM to the 30 µM (Kojima et al., 2016). It can therefore be assumed that the endocrine disrupting effect of RDP/TPP (if proven) could be mediated by these metabolites.
No further *in vivo* data were identified in order to evaluate TPP and/or its hydroxylated metabolites endocrine disruptor properties.

In the current state of knowledge, there is no way to properly evaluate thyroid disrupting properties of TPP and/or its hydroxylated metabolites and thus to estimate the potential contribution of those molecules as RDP metabolites to a possible thyroid disruption.

3.2.6 Environment

3.2.6.1 RDP

There is very little ecotoxicity data for the RDP. The few available data come almost exclusively from study reports of the chemical manufacturer in the chemical safety report (CSR), a report of the Agency of the UK (UK Environment Agency, 2009), a report of US EPA (2014), and a report of Danish EPA (2016). Environmental hazards properties presented are based on those data and on research information found on Scopus and Google Scholar on the date 05 October 2016.

- E-fate and Ecotoxicity of RDP

According to data, RDP exhibits solubility in water ranging from 8.91 µg/L (CSR, n=1 oligomer) to 1.05 mg/L (20 °C) (Fyrolflex, US EPA) or even 10.8 mg/L (CSR, RDP as Fyrolflex). According to US EPA report, the RDP log Kow is 4.9 and 4.93 measured by two independent studies.

Atmospheric photooxidation

According to the UK Environment Agency report, reaction of tetraphenyl resorcinol diphosphate with atmospheric hydroxyl radicals can be estimated of having a half-life for the reaction in air estimated to be 18 hours.

Hydrolysis

Regarding hydrolysis, this report indicates that the half-life of this reaction is 21 d as a worst case at 20°C, in accordance with data reported by the CSR.

No informations are available on the direct photolysis reactions of RDP under environmentally relevant conditions.

- PBT assessment

Concerning Persistence, RDP is considered as a moderate persistent compound based on PBT profiler and one study (CSR). Nevertheless, the commercial mixture Fyrolflex RDP was determined to be inherently biodegradable (OECD 301D). After 28 days, 61% biodegradation occurred. **The substance is considered as not meeting the first stage screening criteria for P and vP**. However, there is concern regarding the fate of RDP because enzymatic or basic hydrolysis leading to the production of phenol (CASRN 108-95-2), diphenyl phosphate (CASRN 838-85-7), and resorcinol (CASRN 108-46-3) through sequential dephosphorylation is theoretically possible but has not been demonstrated.

Regarding Bioaccumulation, a fish BCF of 1300 L/kg is estimated in QSAR medialization by the US EPA. By running the PBTprofiler[7] tool, the same BCF value was obtained (EPI suite v3.0.0[8]). Usually, this value will lead to a classification of moderately bioaccumulative according to CLP criteria, nevertheless the Log Kow (4.9) lead to a higher score. The Danish EPA also recommend a classification as high concern regarding bioaccumulation. Nevertheless, the **substance is considered as not meeting the criteria for B and vB**, but **concern emerge and further data are necessary**. Indeed, the PBT profiler tool also indicate a potency to bioaccumulate especially for n=1 component of the oligomeric complex. New estimations are necessary to obtain more reliable information.

Ecotoxicity data are based on experimental studies and modelization estimations (Danish EPA model, ECOSAR). Parameters as Log Kow and water solubility considered for estimation are different between CSR, US EPA, Danish EPA and UK Environment Agency, leading to some variation in the evaluation. Nevertheless, results are quite similar and give the same indications on RDP potencies.

The following data are available for the different compartments:

- Fish: *Brachydanio rerio* 96-hour LC50= 12.37 mg/L (OECD Guideline 203);

- Invertebrates: *Dapnhia magna* 48-hour EC50= 0.7 mg/L (U.S. EPA, 2010);

Dapnhia magna 48-hour EC50= 0.074 mg/L (OECD 202);

Dapnhia magna 21 d-EC50 = 0.037 mg/L (OECD 211);

Dapnhia magna 21d-NOEC = 0.021 mg/L (OECD 211);

- Algae: *Pseudokirchneriella subcapitata* 96-hour EC50= 48.6 mg/L (OECD Guideline 201)

Pseudokirchneriella subcapitata 72-hour NOEC = 10 mg/L (water accommodated fraction (WAF))

No long-term toxicity data are available for RDP with freshwater or marine fish.

No short-term toxicity are available data for RDP with marine invertebrates.

Regarding the acute toxicity for environment, RDP is assumed to be of very high concern based on measured EC50 values for daphnia, classing it acute toxic cat 1 for environment.
Regarding chronic toxicity for environment, RDP is assumed to be of very high concern based on an experimental 21-day NOEC 0.021 mg/L in Daphnia magna, classing RDP as toxic chronic cat. 2 for environment (due to the lack of data and the easy biodegradability).

Actually, these data indicates that **RDP is considered as not meeting the T criteria**. Nevertheless, estimated ChV values suggest a high hazard with the n

7 PBT Profiler Persistent (P), Bioaccumulative (B), and Toxic (T) Chemical (PBT) Profiler. www.pbtprofiler.net.

8 EPI (EPIWIN/EPISUITE) Estimation Program Interface for Windows, Version 4.0.

=1 oligomer (phosphate esters ECOSAR class)[9] of 0.0093 mg/L for fish. This value is below 0.01 mg/L suggesting a **concern for toxicity** and possibly leading to the classification of RDP as meeting the criteria for T during PBT assessment. On this basis, **new estimations are necessary** to obtain more reliable information, especially chronic test for evaluating the T criteria.

Considering data presented in the CSR and in the literature, RDP is not identified as a PBT. There is some concern about RDP as meeting the PBT criteria especially with uncertainties about water solubility and log Kow parameters. More data are necessary regarding these parameters to remove those uncertainties and new data need to be produced to clarify the potential of RDP as being a PBT chemical.

With the presented data, it is possible to possibly classify the RDP as Aquatic acute tox cat 1 and Aquatic chronic tox 2.

- Endocrine disruptor characteristic of RDP for the environment

Regarding endocrine disruptor concern, no information was identified for environment. No publication dealing on the toxicity of RDP on aquatic or terrestrial organisms are published or made available in EPA Actor, TedXlist, Estrogenic Activity database (FDA), SPIN, Scopus, google scholar, on the date of 05 October 2016. Data available in CSR from Lead registrant, IUCLID and disseminate website from ECHA are not linked to a potential endocrine disruptor of RDP on environment.

3.2.6.2 Resorcinol

Resorcinol is actually under evaluation by the Finnish Safety and Chemical Agency (TUKES) for Sev. According to their primary evaluation for environment, resorcinol is readily biodegradable (97% biodegradation after 4 days in OECD 302B), is not expected to bioaccumulate (Log Kow of 0.8, with a BCF of 3.16, EPI suite). The resorcinol is not considered chronic toxic as regarding the lowest NOEC for aquatic compartment (most sensitive, with 99.8% of distribution), NOEC≥0.172 mg/L (21-d *Daphnia magna* reproduction assay, OECD 211). Regarding the acute toxicity for aquatic compartment, resorcinol is considered as acute tox cat. 1 due to Daphnia magna 48h EC_{50}= 1 mg/L (OECD 202). Soil sorption is assumed to be very low due to a very low Koc of 10.36. The predictive environmental concentration (PEC) are low, and for the most sensitive compartment is of 0.012 / 0.0012 mg/L (freshwater/seawater).

Regarding endocrine disruptor screening, it appeared that resorcinol is a TPO inhibitor, decreasing ITC4 concentration with an EC_{50}= 9.02 mg/L (*Danio rerio* eleutheroembryos OECD 236 draft). Moreover, resorcinol had an impact on TGFD (thyroid gland function disruptor) with a thyroid disrupting index (LC_{50}/EC_{50}) of 61.

According to this preliminary evaluation, we can conclude that resorcinol is Toxic for aquatic compartment with a classification as Acute aquatic tox cat. 1. and chronic tox cat.2 for the environment. There is also evidence of potential for ED effects. More data are necessary to conclude on the ED effect for environment. There is a need to wait the final evaluation of resorcinol by the TUKES for environmental data and

9 ECOSAR/EPI (EPIWIN/EPISUITE) Estimations Programs Interface for Windows, Version 1.11.

potential disrupting effect to draw future recommendations or to draw a final conclusion in this evaluation.

3.2.6.3 TPP

TPP is actually under evaluation by the UK Chemical Agency Health and Safety Executive. Briefly, TPP is currently classified as dangerous for the environment on Annex I of Directive 67/548/EEC and very toxic to aquatic organisms. TPP may cause long-term adverse effects in the aquatic environment. These classification is based on a fish BCF of around 420 l/kg, a 30-day LOEC of 0.037 mg/L for fish and a 96-hour EC50 for invertebrates of 0.25 mg/L (Brooke et al., 2009, US EPA).

Regarding PBT assessment, TPP is readily biodegradable (90% after 28 days, OECD 301 C). Hence, the substance does not meet the P criterion. Regarding the BCF value selected by the UK environment agency, TPP does not meet the B criterion. For the toxicity, the lowest LOEC value from the available tests is 0.037 mg/L, not meeting the T criterion.

The overall conclusion is that the substance does not meet any of the PBT criteria.

Regarding endocrine disruptor screening, a 21-day reproduction study in zebrafish highlight a significant decrease in fecundity, significant increases of plasma 17β-estradiol (E2) concentrations, vitellogenin (VTG) levels, and E2/testosterone (T) and E2/11-ketotestosterone (11-KT) ratios. Sex-dependent changes in transcriptional profiles of several genes of the hypothalamus-pituitary-gonad (HPG) axis where also observable (US EPA).

When focusing on zebrafish plasma in another study, TPP significantly increased plasma E2 in fish and T and 11-KT were decreased (1 mg/L). Changes in transcription of steroidogenic genes and vitellogenin gene were also observed (US EPA).

In conclusion on the ED potential, TPP significantly impaired reproduction in zebrafish (US EPA) and could be considered as being an ED for environment.

3.3 Overall conclusion

Available data on the toxicity of RDP for human health are limited, and are essentially toxicokinetic studies, repeated dose toxicity studies, neurotoxicity studies and developmental and reproductive toxicity studies conducted with the commercial product RDP.

These data showed a possible neurotoxic effect on several species (3 studies in rat and hen), an increase in weight of the adrenal glands, and a possible developmental effect in the rat (a single 2G study available showing a delay in preputial separation and vaginal opening and an increase in weight of the adrenal glands).
Only one toxicity study was conducted with pure RDP. It shows that the exposure of pregnant rabbits by oral gavage from GD6 to GD28 shows fetal malformations at 1000 mg/kg/d.

Data indicate that the production of resorcinol from RDP is possible, but due to the efficiency of phase II metabolic pathways (conjugation), the presence of resorcinol in target tissues should be limited, if any.

The main metabolic pathway of TPP (impurity present up to 5 % in RDP) is hydroxylation to mono- and di-hydroxylated triphenylphosphate and diphenylphosphate.

For the effects on the environment, RDP is not yet identified as a PBT, but there is a real concern that RDP can meet the PBT criteria, and the available data make it is possible to possibly classify RDP as Aquatic acute tox cat. 1 and Aquatic chronic tox cat. 2.

In summary, the limited data available:
- are in favor of a possible neurotoxic effect of RDP;
- are not in favor of a specific effect of resorcinol as metabolite of RDP;
- are not sufficient to decide on a potential PE effect of RDP
- do not exclude the possibility that certain observed effects are due to the specific action of TPP, which exists as impurity (up to 5%) in RDP used in these studies.
- Are in favour of a real concern about RDP as meeting the PBT criteria and classifying it as acute and chronic toxic aquatic.

4 INFORMATION ON (AGGREGATED) TONNAGE AND USES[10]

4.1 Tonnage and registration status

Table 9: Tonnage and registration status

From ECHA dissemination site	
Registrations	☒ Full registration(s) (Art. 10) ☐ Intermediate registration(s) (Art. 17 and/or 18)
Total tonnage band for substance (excluding volume registered under Art 17 or Art 18, or directly exported)	1.000-10.000 tpa

4.2 Overview of uses

Table 10: Uses

	Use(s)

10 *Site accessed on December 2016.*

Uses as intermediate	/
Formulation	Several formulations of materials (for injection, molding, extrusion, compounding…)
Uses at industrial sites	Treatment of textiles and several materials (e.g. cable, pipe, sheet)
Uses by professional workers	Indoor and outdoor use of fire resistant polymers
Consumer Uses	Indoor and outdoor use of fire resistant polymers
Article service life	Indoor and outdoor use of fire resistant polymers

5 JUSTIFICATION FOR THE RISK MANAGEMENT OPTION

Table 11: SVHC Roadmap 2020 criteria

	Yes	No
a) Art 57 criteria fulfilled?	Non-conclusive data	
b) Registrations in accordance with Article 10?	x	
c) Registrations include uses within scope of authorization?		?
d) Known uses not already regulated by specific EU legislation that provides a pressure for substitution?	x	

The effects described in the few available studies appear to be limited and do not allow conclusions to be drawn about the potential risks of RDP to human health and environmental toxicity. Additional data is required.
It is necessary to include RDP in the CoRAP for evaluation. This is justified by the signals highlighted by the existing data on the possibility of neurotoxic and / or reprotoxic and developmental effects.

5.1

5.2 References

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