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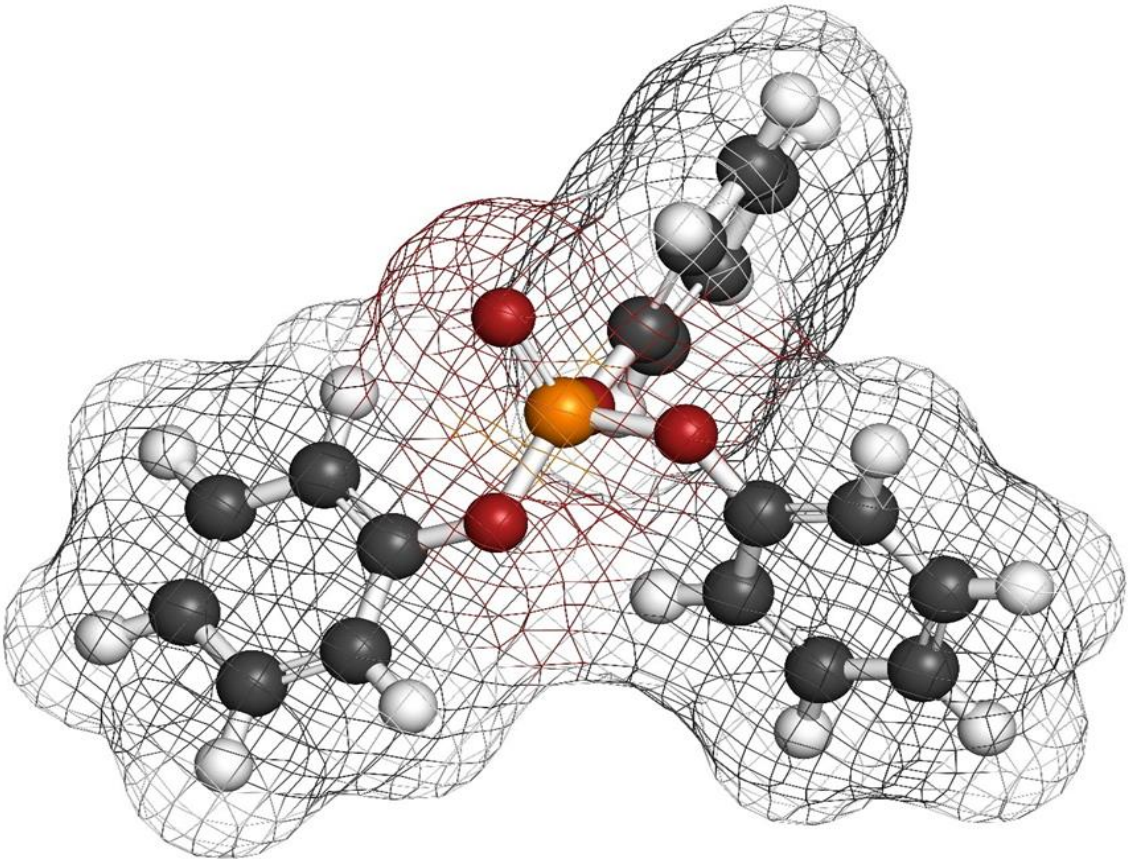
Review of recent literature on tri-substituted phosphate esters. (2015-2016)



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Summary

Research in the field of risk assessment of replacement chemicals for brominated flame retardants is rapidly expanding with more than 70 peer reviewed publication in the international literature published in 2015-2016 alone. These publications show a variety of data including toxicity, environmental levels and persistence or bioaccumulation assessments. Despite this there still is a lack of information for several of the 19 OPFRs included in this literature review. For eleven of the compounds no EDC toxicity data was available but for five no recent acute/chronic toxicity data was found.

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Review of recent literature on tri-substituted phosphate esters (2015-2016)

Oslo, 19 December 2016

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Abbreviations

BBOEP	bis(2-butoxyethyl) phosphate
BCEP	tris(2-chloroethyl) phosphate
BCIPHIPP	1-hydroxy-2-propyl bis(1-chloro-2-propyl) phosphate
BCIPP	bis(1-chloro-2-propyl) phosphate
BDCIPP	bis(1,3-dichloro-2-propyl) phosphate
BDPP	butyl diphenyl phosphate
BFR	brominated flame retardants
CDPhP/CDPP	cresyl diphenyl phosphate
DBP	dibutyl phosphate
DBPP	dibutyl phenyl phosphate
DCP	diphenyl cresyl phosphate
DNBP	di-n-butyl phosphate
DPHP	diphenyl phosphate
dw	dry weight
EHDPP/EHDPHP	2-ethylhexyl diphenyl phosphate
ip-DPHP	isopropyl diphenyl phosphate
IPP	isopropylated triphenyl phosphate
LOD	limit of detection
lw	lipid weight
MPDPP	methylphenyl diphenyl phosphate
nd	not detected
OH-TBOEP	hydroxyl tris(2-butoxyethyl) phosphate
OH-TPHP	hydroxyl triphenyl phosphate
OP	Organophosphorus/organophosphate compound
OPE	Organophosphorus/organophosphate ester
OPFR	Organophosphorus/organophosphate flame retardant
PBDE	Polybrominated diphenyl ethers
PBT	Persistent, Bioaccumulative and Toxic
PFRs	Organophosphorus flame retardants
SPM	suspended particulate matter
TBB	tetrabrominated benzoate
TBEP/TBOEP	tris(2-butoxyethyl) phosphate
TBP/TnBP/TNBP	tri-n-butylphosphate
TBP/TiBP	tri-iso-butylphosphate
TBPh	tetrabrominated phtalate
TBPP	tris(*p*-tert-butylphenyl) phosphate
tb-DPHP	t-butyl diphenyl phosphate
TCEP	tris(2-chloroethyl) phosphate
TCPP/TCIPP	tris(2-chloro-1-methylethyl) phosphate
TDCPP/TDCIPP	tri(1,3-dichloro-2-propyl)phosphate
TCP/TMPP/TCrP	tris(methylphenyl) phosphate / Tricresyl phosphate
TEHP	tris(2-ethylhexyl) phosphate
TEP	triethyl phosphate
TmCP	tris(*m*-methylphenyl) phosphate
ToCP	tris(*o*-methylphenyl) phosphate
TpCP	tris(*p*-methylphenyl) phosphate
TPP/TPHP	triphenyl phosphate
TXP	trixylyl phosphate
ww	wet weight
WWTP	waste water treatment plant

Summary

Research in the field of risk assessment of replacement chemicals for brominated flame retardants is rapidly expanding with more than 70 peer reviewed publication in the international literature in 2015-16. These publications show a variety of data including toxicity, environmental levels and persistence or bioaccumulation assessments. Despite this there still is a lack of information for several of the 19 OPFRs included in this literature review. For 11 of the compounds no EDC toxicity data was available and for 5 no recent acute/chronic toxicity data was found.

Concerning persistence there is more data available for 15 of the 19 compounds, showing that 9 compound might be persistent. This includes the three chlorinated OPFRs (TCEP, TCPP and TDCPP) but also aromatic OPFRs (TBPP, BPPP, DBPP, TXP and IPP).

Only very few measured BCFs are available and most data in the literature is based on QSAR predictions or other model calculations. BCFs were available for all 19 compounds but varied considerably between the different approaches and could easily differ an order of magnitude. Based on the available data two compounds (TEHP and TBPP) were predicted to have an extreme high bioaccumulation potential whereas for four compounds medium (TXP and IPP) or medium to high (EHDPP and TCP) BCF were predicted or calculated.

The 19 OPFRS included in this study were mostly found in the abiotic environment in the indoor environment including air and dust and in water samples mostly in the effluents or near WWTP or in sediments. There is a lot of data on the three chlorinated OPFRs (TCEP, TCPP and TDCPP) in biota and also a reasonable number of studies for TCP, TBP, TPP and TEHP. But much less data on TBPP, BPDPP, BPPP, DBPP, TXP and IPP in biological samples. TEP was only found in one study, BDPP in only a few of a large number of Arctic samples. There is definitely a lack of high quality analytical data for several of the compounds as shown in recent QA/QC studies. One major challenge here is laboratory blank levels of several of the OPFRs in laboratory air. With regard to OPFRs levels it was found not be relevant to normalize to lipids, OPFRs do not seem to accumulate in lipids as traditional persistent organic pollutants (POPs). They seem to behave more like persistent fluor compounds (PFAS) although no information on the accumulation of OPFRs in biota was found.

Of the 19 compounds studied, the aromatic tri substituted OPFRs TXP and IPP are of concern because there is proof of toxicity and predicted bio accumulation. Only very little monitoring data in biota of TXP and IPP exist. In addition, TBOEP is a compound of interest, this compounds have shown EDC toxicity and has recently been found in several biological samples even higher up the food chain.

Sammendrag

Forskning innen risikovurdering av erstatningskjemikalier for bromerte flammehemmere er raskt voksende med mer enn 70 fagfellevurderte publiseringer i internasjonal litteratur (2015-2016). Disse publikasjonene omfatter en rekke studier på toksisitet, nivåer i miljøet, persistens og bioakkumulering. Til tross for dette er det fortsatt mangel på informasjon for flere av de 19 OPFRene inkludert i denne litteraturgjennomgangen. For 11 av forbindelsene er det ingen data tilgjengelig for EDC toksisitet, og for 5 ble ingen nylige data på akutt/kronisk toksisitet funnet.

Når det gjelder persistens er det tilgjengelig data for 15 av de 19 komponentene. Disse viser at 9 av stoffene kan være vedvarende. Dette inkluderer de tre klorerte OPFRene (TCEP, TCPP og TDCPP), men også aromatiske OPFR (TBPP, BPPP, DBPP, TXP og IPP).

Kun svært få målte BCF er tilgjengelige, og de fleste data i litteraturen er basert på QSAR prediksjoner eller andre modellberegninger. Estimerte BCFer var tilgjengelig for alle de 19 komponentene, men varierer betydelig med ulike tilnærminger og kan lett variere en størrelsesorden. Basert på tilgjengelige data ble 2 forbindelser (TEHP og TBPP) spådd å ha et ekstremt høyt bioakkumuleringspotensiale, mens for 4 av forbindelsene er medium (TXP og IPP) eller medium til høy (EHDPP og TCP) BCF spådd eller beregnet.

De 19 OPFRene inkludert i denne studien er for det meste detektert i abiotisk miljø i innemiljø, inkludert i luft, støv og vannprøver, for det meste i avløpsvann, i nærheten av renseanlegg eller i sedimenter. Det finnes mye data på de tre klorerte OPFRene (TCEP, TCPP og TDCPP) i biota og også et rimelig antall studier for TCP, TBP, TPP og TEHP. Men for TBPP, BPDPP, BPPP, DBPP, TXP og IPP i biologiske prøver ble det funnet svært lite eller ingen data. TEP ble bare funnet i en studie, mens BDPP bare ble detektert i noen få av et stort antall arktiske prøver. Det er absolutt mangel på analytiske data av høy kvalitet for flere av forbindelsene som i nyere QA/QC studier. En stor utfordring her er kontaminering på laboratoriene som bidrar til til dels høye nivåer i blank. Med hensyn til nivåer av OPFR ble det funnet å ikke være aktuelt å normalisere til lipider, siden OPFRene ikke ser ut til å hope seg opp i lipider slik som tradisjonelle persistente organiske miljøgifter (POPs). De synes heller å oppføre seg mer som vedvarende fluorforbindelser (PFAS) selv om ingen informasjon om opphopning av OPFR i biota ble funnet.

Av de 19 undersøkte forbindelser, så er de aromatiske trisubstituerte OPFRene TXP og IPP av interesse fordi det er bevis for toksisitet og predikert bioakkumulering. Bare svært lite overvåkingsdata i biota av TXP og IPP eksisterer. I tillegg er TBOEP en forbindelse av interesse, siden denne er vist å ha EDC toksisitet, og nylig er blitt funnet i flere biologiske prøver høyere opp i næringskjeden.

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1 Introduction

1.1 Background

Organophosphorus esters (OPEs) are extensively used as flame retardants, plasticizers and/or anti-foam agents in a wide range of products including textiles, furniture and electronics (Hou et al. 2016, Wei et al. 2015). In particular the increasing demand for alternative flame retardants following the restrictions on the use of penta- and octa-brominated diphenyl ethers (PBDEs) have contributed to their current popularity. Many of the OPEs are frequently present as additives as opposed to being chemically bonded in products. This, in addition to their moderate vapor pressure, results in relatively easy release to the environment via volatilization, leaching and abrasion (Wei et al., 2015). Taking also their persistence into consideration there is no surprise that OPEs are being detected all over the globe in various environmental mediums (Hou et al., 2016).

Current OPEs in use are both halogenated and non-halogenated. Their physical and chemical properties vary, thus their behaviour and fate in the environment are also different. Different chemical property estimation tools to estimate the physical-chemical properties of "novel" organophosphorus flame retardants have been developed (Zhang et al., 2016) and used in different risk assessments (Lassen et al., 2016). A thorough risk assessment on a selected number of OPEs (including triphenyl phosphate (TPP), trixylenyl phosphate (TXP), tricresyl phosphate (TCP), cresyl diphenyl phosphate (CDPhP), tris(isopropylphenyl) phosphate (IPP), isopropylphenyl diphenyl phosphate, tertbutylphenyl diphenyl phosphate (BPDPP), 2-ethylhexyl diphenyl phosphate (EHDPP)) was done by the UK Environment Agency in 2009 (Brooke et al., 2009). Conclusions from these evaluations are that only TXP and IPP potentially meet the PBT criteria in the EU Technical Guidance Document (TGD) for the risk assessment of chemical substances. But still there are several data gaps for not only TXP and IPP but several OPEs included in this review of recent literature and reports.

OPEs show a variety of chemical and physical properties which affect persistence, bioaccumulation and toxicity (PBT) of this compound class. The OPEs included in this study are listed in Table 1. All compounds are either registered or preregistered under REACH.

Table 1: *List of the OPEs included, together with Log P_{ow}/K_{ow}*

	Chemical	Abbreviation	CAS	EC/List no	Log P_{ow}/K_{ow}
1	Tris(2-chloroethyl) phosphate	TCEP	115-96-8	204-118-5	1,44[a]/1,63[b]/1,3[c]
2	Tris(2-chloro-1-methylethyl)phosphate	TCPP/TCIPP	13674-84-5	237-158-7	2,59[a]/2,89[b]/2,6[c]
3	Tri(1,3-dichloro-2-propyl)phosphate	TDCPP/TDCIPP	13674-87-8	237-159-2	3,8[a]/3,65[b]/3,3[c]
4	Tris(2-butoxyethyl) phosphate	TBEP/TBOEP	78-51-3	201-122-9	3,65[a]/3,00[b]/3,8[c]
5	2-ethylhexyl diphenyl phosphate	EHDPP/EHDPHP	1241-94-7	214-987-2	5,37[a]/6,30[b]/6,3[c]
6	Tris(methylphenyl) phosphate / Tricresyl phosphate	TCP/TMPP/TCrP	1330-78-5 (isomer mix)	215-548-8	5,11[a]/5,48[b]/6,1[c]
	Tris(*o*-methylphenyl) phosphate	T*o*CP/*o*-TMPP	78-30-8	201-103-5	
	Tris(*m*-methylphenyl) phosphate	T*m*CP/*m*-TMPP	563-04-2	209-241-8	
	Tris(*p*-methylphenyl) phosphate	T*p*CP/*p*-TMPP	78-32-0	201-105-6	
7	Methylphenyl diphenyl phosphate / Cresyl diphenyl phosphate	CDPhP/DCP/ MPDPP/CDPP	26444-49-5	247-693-8	5,3[c]
8	Tri-n-butylphosphate	TBP/TnBP	126-73-8	204-800-2	4[a]/4,00[b]/2.9[c]
9	Tri-iso-butylphosphate	TBP/TiBP	126-71-6	204-798-3	3,6[a]/3,60[b]/3,5[c]
10	Triphenyl phosphate	TPHP/TPP	115-86-6	204-112-2	4,59[a]/4,70[b]/4,6[c]
11	Tris(2-ethylhexyl) phosphate	TEHP	78-42-2	201-116-6	9,49[a&b]/8,9[c]
12	Tris(*p*-tert-butylphenyl) phosphate	TBPP/TTBPP	78-33-1	201-106-1	9[c]
13	4-tert-Butylphenyl diphenyl phosphate	tBPdPP/BPDPP	56803-37-3	260-391-0	6.6[c]
14	Bis(t-butylphenyl) phenyl phosphate)	bBPPP	65652-41-7	265-859-8	8.3[c]
15	Triethyl phosphate	TEP	78-40-0	201-114-5	0,8[a]/0,87[b]
16	Butyl diphenyl phosphate	BDPP/BDPHP	2752-95-6	220-398-1	4.8[c]
17	Dibutyl phenyl phosphate	DBPP/DBPHP	2528-36-1	219-772-7	4.3[c]
18	Tris(dimethylphenyl) phosphate / Trixylyl/trixylenyl phosphate	TXP/TDMPP	25155-23-1	246-677-8	7,98[b]/7.2[c]
19	Isopropylated triphenyl phosphate	IPP	68937-41-7	273-066-3	7.4[c]

[a]Wei et al., 2015, [b]Hou et al., 2016, [c]Pubchem (www.pubchem.ncbi.nlm.nih.gov)

1.2 Objectives of the present study

There has been a substantial increase in the number of scientific publications dealing with OPs in recent years but for risk assessment in terms of PBT properties, data for a large number of OPEs is still lacking. The Norwegian Environment Agency has identified the need for a review of the most recent literature on the PBT behavior of tri substituted phosphate esters often used as organophosphate flame retardants (OPFRs). The number of hits searching for "organophosphorus flame retardants" in PubMed has increased from 8 in 2005-2006 to 58 in 2015-2016 (http://www.ncbi.nlm.nih.gov/pubmed) and from 7 to 119 when searching for "organophosphate flame retardants" (searches performed on 01.08.2016). This report summarizes the current knowledge to rank the different flame retardants with regards to PBT properties.

2 Occurrence & levels

2.1 Abiotic samples

OPFRs are found in relatively high concentrations (mg/g) in many different consumer products. They are present as additives in most products and are not chemically bonded. This means that products that contain these substances are highly likely to be sources of OPFRs to the environment. As a consequence, several OPFRs have been found in both indoor and outdoor environments, in matrices such as air, water and soil (reviewed by Wei et al., 2015). In this report only a summary of literature from 2015 and 2016 is included for abiotic matrices.

Air

Recent data includes the determination of 9 OPFRs (TEP, TPP, TiBP, TnBP, TBEP, TEHP, TCEP, TCPP and TDCPP) in indoor (private homes, private cars, schools, offices, day care centers, building material markets and floor/carpet stores) and outdoor air samples from the Rhine/Main area, Germany (Zhou et al., 2016). Total OPFR concentrations (ΣOPFRs) in indoor air ranged from 3.30 to 751 ng/m^3 with a median of 40.23 ng/m^3, which was approximately eight times higher than those in outdoor air (median 5.38 ng/m^3). This indicates that the indoor environment poses a large exposure risk. Another Chinese study by Luo et al. (2016) analysed atmospheric size-fractionated particles at different heights in an e-waste recycling zone (QY) and urban Guangzhou (GZ) for OPFRs. The total air concentrations of eight OPFRs (TiBP, *TNBP*, TCEP, TCIPP, TDCPP, TPHP, TBOEP and EHDPP) were 130 ± 130 and 138 ± 127 ng/m^3 in QY and GZ, respectively. Venier et al. (2015) analysed air collected on the shores of the Great Lakes. Levels of the twelve OPs measured ranged from about 1500 pg/m^3 in Chicago and Cleveland to about 100 pg/m^3 at Eagle Harbor. This was about 100, 1200, and 600 times higher (on average) than the PBDE, TBB, and TBPh concentrations, respectively. A study of human external exposure to OPFRs via air, dust and hand wipes was done by Xu et al. (2016). Samples were collected from 61 participants and their houses. Median levels of ∑OPFRs (sum of TEHP, TNBP, EHDPHP, TCEP, TBOEP, TPHP, TMPP, TDCIPP and TCPP) were 44 (range: 12-183) ng/m^3 for personal ambient air, 163 (range: 28-1018) ng/m^3 for indoor stationary air, 20 500 (range: 3662-505 000) ng/g for floor dust, 33 100 (range: 5800-1 490 000) ng/g for surface dust and 192 (range: 20-14 100) ng for hand wipes. TCPP was frequently detected in all matrices (detection frequency > 85%), indicating its ubiquitous presence in indoor environment and its wide application in commercial products. TBOEP was commonly detected in high concentrations in dust and hand wipes, but not in air. Another study focusing on inhalation exposure of humans was conducted on 10 adults from Washington State, USA (Schreder et al., 2016). TCPP, TDCPP and TCEP had median concentrations in inhalable (>4 μm) particulate fraction of 262 (range: 16-1180) ng/m^3, 0.75 (range: <1.5-82.2) ng/m^3 and 11.1 (range: <1.5-77.8) ng/m^3, respectively. In the respirable particulate fraction (<4 μm) the median concentrations were 10.8 (range: <1.5-28.6) ng/m^3 for TCPP, 2.0 (range: <1.5-20.9) ng/m^3 for TDCPP and only nd for TCEP.

Waste water treatment plants

O'Brien et al. (2015) analysed waste water (raw inlet) from eleven different waste water treatment plants. TBOEP had the highest concentrations which ranged from 0.4 to 6.6 μg/L with a median of 4.4 μg/L followed by TCIPP, (0.5–4.1 μg/L, median = 2.5 μg/L), TIBP (1.1–1.6 μg/L with a median of 1.4 μg/L), TCEP (0.2–0.6 μg/L with a median of 0.3 μg/L) and TDCIPP (0.05–0.3 μg/L with a median of 0.1 μg/L). Liang et al. (2016) investigated the fate of 14 different organophosphate esters (OPEs) in an advanced municipal sewage treatment plant. They found OPEs in all sewage water and sludge samples with total OPEs (ΣOPEs) concentrations of 1399 ± 263 ng/L in raw sewage aqueous phase, 833 ± 175 ng/L in tertiary effluent aqueous phase, and 315 ± 89 ng/g dry weight in dewatered sludge. The dissolved concentrations of ΣOPEs significantly decreased during biological treatment, whereas negligible decrease was observed in mechanical and physical-chemical treatments. Further they confirmed some general differences: (1) OPEs with long chains (i.e. TnBP, TBEP) are degraded more easily than those with short chains (i.e. TEP); (2) chlorinated hydrocarbon chains are more resistant to biodegradation than non-chlorinated chains, and (3) branched chains and phenyl/tolyl chains are less amendable to biodegradation than unbranched chains. Gao et al. (2016) reported concentrations of both OP triesters and diesters in

sludge from sewage treatment plants (STPs) in Beijing. TPhP, T*m*CP, TBEP, TEHP and TnBP were detected in all 43 samples (from 8 different STPs and 5 different time points) in concentrations ranging from 1.20-3550 µg/kg dry weight (dw), with a median sum of 14 OP triesters of 521 µg/kg dw. TEP, TCEP, CDPP (cresyl diphenyl phosphate), EHDPP, TDCP and TiBP were present in more than 50% of the samples and had median concentrations ranging from 3.8-21.4 µg/kg dw. Pang et al. (2016) analysed sewage sludge from 24 WWTPs of 18 cities in Henan province Central China. They found TBEP (1.6-383 µg/kg dw), TCEP (2.5-203 µg/kg dw), TnBP (3.5-197 µg/kg dw), TPhP (4.4-46.4 µg/kg dw) and TCPP (6.7-161 µg/kg dw) in all samples, and TDCP (<LOD-48.4 µg/kg dw) in 95.8% of the samples.

River water

Gorga et al. (2015) analysed water and sediments from Iberian rivers where they detected TBEP in all water samples in the range 5.3-659 ng/L and nd-66 ng/g dw in sediment. TCPP was found in the highest levels ranging from nd-6377 ng/L in water and nd-459 ng/g dw in sediment. TCEP was in the ranges nd-232 ng/L in water samples and nd-54 ng/g dw in sediment. Wang R. et al. (2015) determined the occurrence and spatial distribution of 11 organophosphate esters in 40 major rivers entering into the Bohai Sea. Total OPEs ranged from 9.6 to 1549 ng/L, with an average of 300 ng/L. TCPP (4.6-921 ng/L, mean: 186 ng/L) and TCEP (1.3-268 ng/L, mean: 80.2 ng/L) were the most abundant OPEs.

Drinking water

Khan et al. (2016) analysed potable water from industrial, rural and background areas in Pakistan. The minimum and maximum OPFR concentrations in the potable water samples were nd-71.05 ng/L from the industrial sites, nd-12.06 ng/L from rural sites and nd-0.08 ng/L from background zones. TCPP, TCEP, TDCPP, TPP, TEHP and TBP were detected in 64.4%, 18.5%, 10.5%, 3.0%, 2.6% and 0.9% of the samples respectively. Lee et al. (2016) determined OPFRs in drinking water (purified water, tap water and bottled water) from Korea. ∑OPFRs (including results for TEP, TBP, TCEP, TCPP, TDCPP, TBEP, TPP, EHDPP, TEHP and TCP) were in the range nd-1660 ng/L with a mean of 140 ± 245 ng/L. The highest detection frequency was for TCPP (82%), TCEP (75%) and TBEP (59%). ∑OPFRs were significantly higher in purified water (median: 101 ng/L) and bottled water (median: 104 ng/L) compared to tap water. TCPP and TBEP showed the same pattern, while concentrations of TCEP did not differ significantly between the different types of drinking water. This study also revealed that water purification systems can be a source of OPFR contamination. Elevated levels of TCPP were detected in the head (2300 mg/g in part) and O-ring (45,000 mg/g in part) of a system, indicating that the release of TCPP from these components can contribute to water contamination.

Soil

Matsukami et al. (2015) detected TPHP, EHDPP, TMPP, TCEP, TCIPP and TDCIPP (TPHP highest with concentrations in the range <LOQ-3300 ng/g dw) in surface soil samples from an non authorized e-waste recycling area in northern Vietnam. The detection rate was between 40-100% in the e-waste recycling workshop but only 0-5% in the rice paddy's nearby. In river sediment samples TPHP was found in samples from all three sampling sites in the e-waste recycling area, while TMPP, TCIPP and TDCIPP were above LOQ in one sample from this area. In upstream sediment samples all OPFRs were below LOQ, and only TPHP were detected at the downstream sampling point closest to the recycling area. Brandsma et al. (2015) detected OPFRs in sediment and SPM samples from the Western Scheldt, the Netherlands. TCEP, TCIPP, TDCIPP, TPHP, TiBP, TBOEP, TMPP, EHDPP and TEHP were all detected in both sediment and SPM. TBOEP, TiBP and TCIPP were the dominant compounds in sediment with median concentrations of 7, 8.1 and 1.8 ng/g dw, respectively. In the SPM samples the levels of OPFRs were 3-32 times higher than in the sediment samples, with the exception of TiBP which was 8 times lower. TBOEP and TCIPP were the dominating compounds in SPM with median concentrations of 33 and 16 ng/g dw, respectively.

In summary OPFRs were found both in the air and water environment especially in effluent and sludge from waste water treatment facilities and in soil. This also evident from recent data from Miljødirektoratet 2014, 2015, 2016 within the Environmental Contaminants in an Urban Fjord project. Several OFPRs were found in storm water, snow and sediment including the chlorinated OPFRs (TCEP, TCPP and TDCPP) aromatic OPFRs (DBPP, BDPP, TPP, EHDPP, TCP), and aliphatic OPFRs (TBP, TEHP, and TBOEP).

A compilation of Norwegian sceening data in 'Compilation of Norwegian Screening Data for Selected Contaminants (2002 – 2012)' from the Klima- og Forurensningsdirektoratet 2012 showed the same trend with detectable levels of the chlorinated OPFRs in all water and WTP samples and in a majority of the sediment samples. From the aromatic OFPRs, DBPhP, EHDPP, TPP and TCP were detected in all WTP samples and several of the water samples. DPhDP and CDPP were not detected in any of the Nordic samples. Also TEP and TEHP were not found or in concentrations only just above the LOD for limited number of water related samples. TBOEP was found in water, sediment and WTP samples.

2.2 Biota

Wei et al., 2015 reviewed data on the occurrence of OPFRs in biota from studies before 2015. They found limited information on their occurrence in fish, mussels, domestic birds, human milk and pine needles. More studies have been published in 2015 and 2016 that have focused on the occurrence of OPFRs in the environment, wildlife and humans. This data is summarized below.

2.2.1 TCEP

TCEP has previously been detected in human milk from Sweden, fish from Sweden and China, mussels from Sweden, domestic birds from China and in pine needles from USA (Wei et al., 2015).
Brandsma et al. (2015) determined TCEP in different species from an estuarine food web in the Western Scheldt in the Netherlands. TCEP was detected in common shore crab, lugworm, goby, sculpin, herring and in 1 of 5 samples of pouting. Median concentrations were all below 1 ng/g ww. TCEP was in this study not detected in cockle, sole, plaice, phytoplankton, zooplankton/jelly fish nor in common tern eggs.
Herring gull eggs from five different colonial nesting sites taken in the period 1990-2010 from the Laurentian Great Lakes of North America contained TCEP in the range nd-3.32 ng/g ww (Greaves et al., 2016). Hallanger et al. (2015) screened eight arctic species for 14 OPFRs. TCEP was detected in capelin (whole body, range: nd-9.41 ng/g lw), kittiwake (liver, range: nd-12.9 ng/g lw), only one of twelve glaucous gulls (egg, 10.8 ng/g lw), only one of ten harbor seals (plasma, 3.51 ng/g lw) and in only two of twenty polar bears (plasma, 1.91 and 52.5 ng/g lw). In eggs from Brünnich's guillemot (n=10), blubber from ringed seals (n=10) and liver from arctic fox (n=10) TCEP was below the detection limit. Malarvannan et al. (2015) investigated the levels, profiles and human health risk of organophosphorus flame retardants and plasticizers (PFRs) in wild European eels from fresh water bodies in the highly populated and industrial Flanders region (Belgium). In this study the median value for total OPFRs in muscle for the 26 sites investigated was 44 ng/g lw (8.4 ng/g ww), whereof TCEP constituted only 1%. Muscle tissues from Nile tilapia from an e-waste processing area in northern Vietnam was analysed for both monomeric and oligomeric OPFRs. Concentration range for TCEP was <15-160 ng/g lw with median of 46 ng/g lw (n=15) (Matsukami et al., 2016). TCEP was detected in all chicken egg samples taken from an e-waste recycling region in China (Zheng et al., 2016). Median concentrations for the four different sites studied were 1.08, 0.67, 0.72 and 0.65 ng/g ww (the latter being the control site).
Several recent studies have looked into the exposure of humans to OPFRs. Ding et al. (2016) determined 12 OPEs in human placenta collected in Eastern China. TCEP in these samples had a median concentration of 142 ng/g lw, range nd-515 ng/g lw and a detection frequency of 92%. Pooled human serum samples from residents of Shandong, China taken in 2011 and 2015 were analysed for 6 OPFRs (Ma et al., 2016). Median concentrations of TCEP in these samples were 552 ng/g lw in 2011 and 603 ng/g lw in 2015. Qiao et al. (2016) analysed human hair to assess exposure to OPFRs. Samples from 49 volunteer participants from Guangzhou, China were taken in 2014. Levels of TCEP in hair was in the range <3.5-64.9 ng/g dw with median 3.6 ng/g dw and a detection frequency of 57%. No TCEP was detected in the serum samples. OPFRs were also investigated in 50 rice samples, 75 commonly consumed foods and 45 human hair samples from China (Zhang et al., 2016). Median concentration for TCEP in rice (n=50) was 15.3 ng/g (range: nd-123, detection frequency: 88%). In various food items (beverages, dairy products, grains, vegetables, meat and fruits) median concentration of TCEP was in the range 0.01 ng/g (meat)-220 ng/mL (beverages) with detection frequencies of 90-100%, except for meat where it was 71%. In the human hair samples the median

concentration of TCEP was 1.42 ng/g dw (range: nd-14 ng/g dw, detection frequency: 53%). Abdallah et al. 2016 investigated human dermal absorption of the chlorinated OPEs; TCEP, TCIPP and TDCIPP using human ex vivo skin and EPISKIN™ models. These experiments revealed 28% absorption of the applied dose (500 ng/cm², finite dose) for TCEP after 24 h exposure. This might indicate that dermal absorption of this substance may play a role in the overall exposure of humans.

2.2.2 TCPP/TCIPP

TCPP/TCIPP has previously been detected in human milk from Sweden, fish from Sweden and China, mussels from Sweden, domestic birds from China and pine needles from USA (Wei et al., 2015).
Brandsma et al. (2015) determined TCIPP in different species from an estuarine food web in the Western Scheldt in the Netherlands. TCIPP was detected in phytoplankton, cockle, common shore crab, plaice, goby, sculpin, herring, zooplankton/jelly fish and in pouting. Median concentrations ranged from 0.99 (zooplankton/jelly fish)-4.6 (sculpin) ng/g ww. TCIPP was in this study not detected in lugworm, sole nor in common tern eggs.
Herring gull eggs from five different colonial nesting sites taken in the period 1990-2010 from the Laurentian Great Lakes of North America contained TCIPP in the range nd-2.84 ng/g ww (Greaves et al., 2016). In the same study, TCIPP was detected in the range nd-4.4 ng/g ww in different food web samples (lake trout, rainbow smelt, slimy sculpin, round goby, deepwater sculpin, alewife, mysis, net plankton, herring gull eggs, walleye, emerald shiner, trout perch, yellow perch, white perch and freshwater drum) collected in 2010. Hallanger et al. (2015) screened eight arctic species for 14 OPFRs. TCIPP was detected in capelin (whole body, 36.6-92.9 ng/g lw) and only two of ten harbour seals (plasma, nd-372 ng/g lw). In liver from kittiwake (n=12), eggs from Brünnich's guillemot (n=10), eggs from glaucous gull (n=12), blubber from ringed seals (n=10), liver from arctic fox (n=10) and plasma from polar bears (n=20) TCIPP was below the detection limit. Malarvannan et al. (2015) investigated the levels, profiles and human health risk of organophosphorus flame retardants and plasticizers (PFRs) in wild European eels from fresh water bodies in the highly populated and industrial Flanders region (Belgium). In this study the median value for total OPFRs in muscle for the 26 sites investigated was 44 ng/g lw (8.4 ng/g ww), whereof TCIPP constituted as much as 64%. Muscle tissues from Nile tilapia from an e-waste processing area in northern Vietnam was analysed for both monomeric and oligomeric OPFRs. Concentration range for TCIPP was 63-300 ng/g lw with median of 130 ng/g lw (n=15) (Matsukami et al., 2016). TCIPP was detected in most chicken egg samples taken from an e-waste recycling region in China (Zheng et al., 2016). Median concentrations for the four different sites studied were 0.56, 0.37, 0.33 and 0.17 ng/g ww (the latter being the control site).
Several recent studies have looked into the exposure of humans to OPFRs. Ding et al. (2016) determined 12 OPEs in human placenta collected in Eastern China. TCPP in these samples were in the concentration range nd-215 ng/g lw and had a detection frequency of 50%. Qiao et al. (2016) analysed human hair and serum to assess exposure to OPFRs. Samples from 49 volunteer participants from Guangzhou, China were taken in 2014. Levels of TCIPP in hair was in the range <6.5-141 ng/g dw with median 43.9 ng/g dw and a detection frequency of 98%. No TCIPP was detected in the serum samples. OPFRs were also investigated in 50 rice samples, 75 commonly consumed foods and 45 human hair samples from China (Zhang et al., 2016). Median concentration for TCIPP in rice (n=50) was 4.5 ng/g (range: nd-84.9, detection frequency: 88%). In various food items (beverages, dairy products, grains, vegetables, meat and fruits) median concentration of TCIPP was in the range nd (meat)-104 ng/mL (beverages) with detection frequencies of 80-100%, except for meat where it was 43%. In the human hair samples (n=45) the median concentration of TCIPP was 0.28 ng/g dw (range: nd-13.3 ng/g dw, detection frequency: 56%). Abdallah et al. 2016 investigated human dermal absorption of the chlorinated OPEs; TCEP, TCIPP and TDCIPP using human ex vivo skin and EPISKIN™ models. These experiments revealed 25% absorption of the applied dose (500 ng/cm², finite dose) for TCIPP after 24 h exposure. This might indicate that dermal absorption of this substance may play a role in the overall exposure of humans.

2.2.3 TDCPP/TDCIPP

TDCPP/TDCIPP has previously been detected in human milk from Sweden, fish from Sweden and China, domestic birds from China and pine needles from USA (Wei et al., 2015).
Brandsma et al. (2015) determined TDCIPP in different species from an estuarine food web in the Western Scheldt in the Netherlands. TDCIPP was detected in cockle, lugworm, phytoplankton and in zooplankton/jelly fish. Median concentrations were all below 1 ng/g ww. TDCIPP was in this study not detected in common shore crab, goby, sole, plaice, sculpin, herring, pouting nor in common tern eggs.
Herring gull eggs from five different colonial nesting sites taken in the period 1990-2010 from the Laurentian Great Lakes of North America did not contain TDCIPP above the detection limit (Greaves et al., 2016). In the same study, TDCIPP was detected only in plankton (0.63 ng/g ww) among the different food web samples (lake trout, rainbow smelt, slimy sculpin, round goby, deepwater sculpin, alewife, mysis, net plankton, herring gull eggs, walleye, emerald shiner, trout perch, yellow perch, white perch and freshwater drum) collected in 2010. Hallanger et al. (2015) screened eight arctic species for 14 OPFRs. TDCIPP was detected in only one of ten capelins (whole body, 9.6 ng/g lw), two of twelve glaucous gulls (egg, nd-29.5 ng/g lw) and in four of twenty polar bears (plasma, nd-6.89 ng/g lw). In liver from kittiwake (n=12), eggs from Brünnich's guillemot (n=10), blubber from ringed seals (n=10), plasma from harbor seal (n=10) and liver from arctic fox (n=10) TDCIPP was below the detection limit. Malarvannan et al. (2015) investigated the levels, profiles and human health risk of organophosphorus flame retardants and plasticizers (PFRs) in wild European eels from fresh water bodies in the highly populated and industrial Flanders region (Belgium). In this study the median value for total OPFRs in muscle for the 26 sites investigated was 44 ng/g lw (8.4 ng/g ww), whereof TDCPP constituted only 1%. Muscle tissues from Nile tilapia from an e-waste processing area in northern Vietnam was analysed for both monomeric and oligomeric OPFRs. Concentration range for TDCIPP was 12-79 ng/g lw with median of 27 ng/g lw (n=15) (Matsukami et al., 2016). TDCIPP was detected in about 50% of the chicken egg samples taken from an e-waste recycling region in China (Zheng et al., 2016). Concentration ranges for the four different sites studied were <0.60-5.84, <0.60-13.1, <0.60-1.95 and 0.67 ng/g ww (the latter being the control site where only one sample were above LOQ).
Several recent studies have looked into the exposure of humans to OPFRs. Ding et al. (2016) determined 12 OPEs in human placenta collected in Eastern China. TDCIPP in these samples were in the concentration range nd-82.8 ng/g lw and had a detection frequency of 44%. Qiao et al. (2016) analysed human hair and serum to assess exposure to OPFRs. Samples from 49 volunteer participants from Guangzhou, China were taken in 2014. Levels of TDCIPP in hair was in the range <1.04-73.8 ng/g dw with median 4.14 ng/g dw and a detection frequency of 86%. No TDCIPP was detected in the serum samples. OPFRs were also investigated in 50 rice samples, 75 commonly consumed foods and 45 human hair samples from China (Zhang et al., 2016). Median concentration for TDCIPP in rice (n=50) was 0.25 ng/g (range: nd-31.3, detection frequency: 84%). In various food items (beverages, dairy products, grains, vegetables, meat and fruits) median concentration of TDCIPP was in the range nd (meat)-85.1 ng/mL (dairy products) with various detection frequencies ranging from 43% (meat) to 100% (grains and fruits). In the human hair samples the median concentration of TDCIPP was 0.54 ng/g dw (range: 0.04-4.71 ng/g dw, detection frequency: 100%). Abdallah et al. 2016 investigated human dermal absorption of the chlorinated OPEs; TCEP, TCIPP and TDCIPP using human ex vivo skin and EPISKIN™ models. These experiments revealed 13% absorption of the applied dose (500 ng/cm^2, finite dose) for TDCIPP after 24 h exposure. This might indicate that dermal absorption of this substance may play a role in the overall exposure of humans.

2.2.4 TBEP/TBOEP

TBEP/TBOEP has previously been detected in human milk from Sweden, fish from China and the Philippines, perch close to sources in Sweden and domestic birds from China (Wei et al., 2015).
Brandsma et al. (2015) determined TBOEP in different species from an estuarine food web in the Western Scheldt in the Netherlands. TBOEP was detected in common shore crab, cockle, sole, plaice, goby, sculpin, herring and in pouting. Median concentrations were in the range 1.3 (cockle)-17 (sculpin) ng/g ww. TBOEP was in this study not detected in lugworm, phytoplankton, zooplankton/jelly fish nor in common tern eggs.

Herring gull eggs from five different colonial nesting sites taken in the period 1990-2010 from the Laurentian Great Lakes of North America contained TBOEP in the range nd-3.8 ng/g ww (Greaves et al., 2016). In the same study, TBOEP was detected in the range nd-13.5 ng/g ww in different food web samples (lake trout, rainbow smelt, slimy sculpin, round goby, deepwater sculpin, alewife, mysis, net plankton, herring gull eggs, walleye, emerald shiner, trout perch, yellow perch, white perch and freshwater drum) collected in 2010. Hallanger et al. (2015) screened eight arctic species for 14 OPFRs. TBOEP was detected in one of ten capelin (whole body, 537 ng/g lw) and in arctic fox (liver, nd-2198 ng/g lw). In liver from kittiwake (n=12), eggs from Brünnich's guillemot (n=10), eggs from glaucous gull (n=12), blubber from ringed seals (n=10), plasma from harbor seals (n=10) and plasma from polar bears (n=20) TBOEP was below the detection limit. Malarvannan et al. (2015) investigated the levels, profiles and human health risk of organophosphorus flame retardants and plasticizers (PFRs) in wild European eels from fresh water bodies in the highly populated and industrial Flanders region (Belgium). In this study the median value for total OPFRs in muscle for the 26 sites investigated was 44 ng/g lw (8.4 ng/g ww), whereof TBOEP constituted 5%. TBOEP was not detected in any of the chicken egg samples taken from an e-waste recycling region in China (Zheng et al., 2016).
Several recent studies have looked into the exposure of humans to OPFRs. Ding et al. (2016) determined 12 OPEs in human placenta collected in Eastern China. TBEP in these samples had a median concentration of 16.7 ng/g lw, range nd-77.8 ng/g lw and a detection frequency of 84%. OPFRs were also investigated in 50 rice samples, 75 commonly consumed foods and 45 human hair samples from China (Zhang et al., 2016). Median concentration for TBOEP in rice (n=50) was 1.18 ng/g (range: nd-62.6, detection frequency: 94%). In various food items (beverages, dairy products, grains, vegetables, meat and fruits) median concentration of TBOEP was in the range nd (meat)-2.91 ng/mL (beverages) with various detection frequencies ranging from 43% (meat) to 100% (fruits). In the human hair samples the median concentration of TBOEP was 0.13 ng/g dw (range: nd-2.93 ng/g dw, detection frequency: 80%).

2.2.5 EHDPP/EHDPHP

EHDPP/EHDPHP has previously been detected in human milk from Sweden, fish from Sweden, China and the Philippines, mussels from Sweden and domestic birds from China (Wei et al., 2015).
Brandsma et al. (2015) determined EHDPP in different species from an estuarine food web in the Western Scheldt in the Netherlands. EHDPP was detected in lugworm, phytoplankton, zooplankton/jelly fish. Median concentrations were in the range 0.27 (zooplankton/jelly fish)-2.2 (phytoplankton) ng/g ww. EHDPP was in this study not detected in cockle, common shore crab, sole, plaice, goby, sculpin, herring, pouting nor in common tern eggs.
EHDPP was not detected in any of the herring gull eggs taken from five different colonial nesting sites in the period 1990-2010 from the Laurentian Great Lakes of North America (Greaves et al., 2016). Nor in the different food web samples (lake trout, rainbow smelt, slimy sculpin, round goby, deepwater sculpin, alewife, mysis, net plankton, herring gull eggs, walleye, emerald shiner, trout perch, yellow perch, white perch and freshwater drum) collected in 2010 in the same study was EHDPP detected. Hallanger et al. (2015) screened eight arctic species for 14 OPFRs. EHDPP was detected in capelin (whole body, range: 11.1-485 ng/g lw), kittiwake (liver, range: nd-136 ng/g lw) and in only one of ten ringed seals (blubber, 9.6 ng/g lw). In eggs from Brünnich's guillemot (n=10), eggs from glaucous gulls (n=12), plasma from harbor seals (n=10), liver from arctic fox (n=10) and plasma from polar bears (n=20) TBOEP was below the detection limit. Malarvannan et al. (2015) investigated the levels, profiles and human health risk of organophosphorus flame retardants and plasticizers (PFRs) in wild European eels from fresh water bodies in the highly populated and industrial Flanders region (Belgium). In this study the median value for total OPFRs in muscle for the 26 sites investigated was 44 ng/g lw (8.4 ng/g ww), whereof EHDPP constituted 12%. Muscle tissues from Nile tilapia from an e-waste processing area in northern Vietnam was analysed for both monomeric and oligomeric OPFRs. Concentration range for EHDPP was <5-11 ng/g lw with detection frequency of only 20% (n=15) (Matsukami et al., 2016). EHDPHP was detected in less than 50% of the chicken egg samples taken from an e-waste recycling region in China (Zheng et al., 2016). Concentration ranges and detection frequencies for the four different sites studied were <0.30-0.40 (17%), <0.30-0.38 (28%), <0.30-0.68 (40%) and <0.30-0.83 (50%) ng/g ww (the latter being the control site).

Several recent studies have looked into the exposure of humans to OPFRs. Ding et al. (2016) determined 12 OPEs in human placenta collected in Eastern China. EHDPP in these samples were in the concentration range nd-145 ng/g lw and had a detection frequency of 20%. Qiao et al. (2016) analysed human hair and serum to assess exposure to OPFRs. Samples from 49 volunteer participants from Guangzhou, China were taken in 2014. Levels of EHDPP in hair was in the range <5.9-78.0 ng/g dw with median 16.6 ng/g dw and a detection frequency of 71%. No EHDPP was detected in the serum samples.

2.2.6 TCP/TMPP

TCP/TMPP has previously been detected in human milk from Sweden, fish from Sweden and the Philippines and mussels from Sweden (Wei et al., 2015).
Brandsma et al. (2015) determined TMPP in different species from an estuarine food web in the Western Scheldt in the Netherlands. TMPP was detected in lugworm and in phytoplankton. Median concentrations were below 1 ng/g ww for both species. TMPP was in this study not detected in cockle, common shore crab, sole, plaice, goby, sculpin, herring, zooplankton/jelly fish, pouting nor in common tern eggs.
TMPP was not detected in any of the herring gull eggs taken from five different colonial nesting sites in the period 1990-2010 from the Laurentian Great Lakes of North America (Greaves et al., 2016). Nor in the different food web samples (lake trout, rainbow smelt, slimy sculpin, round goby, deepwater sculpin, alewife, mysis, net plankton, herring gull eggs, walleye, emerald shiner, trout perch, yellow perch, white perch and freshwater drum) collected in 2010 in the same study was TMPP detected. Hallanger et al. (2015) screened eight arctic species for 14 OPFRs. TCP was detected in capelin (whole body, range: nd-23.7 ng/g lw) and in harbor seals (plasma, nd-14.9 ng/g lw). In liver from kittiwake (n=12), eggs from Brünnich's guillemot (n=10), eggs from glaucous gulls (n=12), blubber from ringed seals (n=10), liver from arctic fox (n=10) and plasma from polar bears (n=20) TCP was below the detection limit. Muscle tissues from Nile tilapia from an e-waste processing area in northern Vietnam was analysed for both monomeric and oligomeric OPFRs. Concentration range for TMPP was 11-94 ng/g lw with median of 37 ng/g lw (n=15) (Matsukami et al., 2016). TMPP was not detected in any of the chicken egg samples taken from an e-waste recycling region in China (Zheng et al., 2016).
Several recent studies have looked into the exposure of humans to OPFRs. Ding et al. (2016) determined 12 OPEs in human placenta collected in Eastern China. TCrP in these samples had a median concentration of 5.4 ng/g lw, range nd-73.3 ng/g lw and a detection frequency of 84%. Pooled human serum samples from residents of Shandong, China taken in 2011 and 2015 were analysed for 6 OPFRs (Ma et al., 2016). Median concentrations of *o*-TMPP, *m*-TMPP and *p*-TMPP in these samples were 0.28, 9.66 and 1.80 ng/g lw in 2011 and 0.13, 7.04 and 0.68 ng/g lw in 2015, respectively.

2.2.7 CDPhP/CDPP/MPDPP

Muscle tissues from Nile tilapia from an e-waste processing area in northern Vietnam was analysed for both monomeric and oligomeric OPFRs. Concentration range for MPDPP was 11-68 ng/g lw with median of 24 ng/g lw (n=15) (Matsukami et al., 2016).

2.2.8 TBP/TnBP/TiBP

TBP/TnBP has previously been detected in human milk from Sweden, fish from Sweden, China and the Philippines, mussels from Sweden and domestic birds from China (Wei et al., 2015).
Brandsma et al. (2015) determined TiBP in different species from an estuarine food web in the Western Scheldt in the Netherlands. TiBP was detected in lugworm, goby, sculpin and in pouting. Median concentrations were in the range 0.55 (sculpin)-7.4 (goby) ng/g ww. TiBP was in this study not detected in cockle, common shore crab, sole, plaice, herring, phytoplankton, zooplankton/jelly fish nor in common tern eggs.
Herring gull eggs from five different colonial nesting sites taken in the period 1990-2010 from the Laurentian Great Lakes of North America did not contain TnBP above the detection limit (Greaves et al., 2016). In the same study, TnBP was detected in lake trout (nd-0.20 ng/g ww), alewife (nd-0.06 ng/g ww),

mysis (1.12 ng/g ww) and plankton (0.63 ng/g ww) among the different food web samples (lake trout, rainbow smelt, slimy sculpin, round goby, deepwater sculpin, alewife, mysis, net plankton, herring gull eggs, walleye, emerald shiner, trout perch, yellow perch, white perch and freshwater drum) collected in 2010. Hallanger et al. (2015) screened eight arctic species for 14 OPFRs. TBP was not detected in any samples, while TiBP was detected in only one of ten harbor seals (plasma, range: 7.44 ng/g lw) and in only four of twenty polar bears (plasma, nd-10 ng/g lw). In whole body capelins (n=10), liver from kittiwake (n=12), eggs from Brünnich's guillemot (n=10) and glaucous gull (n=12), blubber from ringed seals (n=10) and liver from arctic fox (n=10) TiBP was below the detection limit. TNBP was not detected in any of the chicken egg samples taken from an e-waste recycling region in China (Zheng et al., 2016).
Several recent studies have looked into the exposure of humans to OPFRs. Ding et al. (2016) determined 12 OPEs in human placenta collected in Eastern China. TnBP in these samples were in the concentration range nd-100 ng/g lw and had a detection frequency of 46%. Pooled human serum samples from residents of Shandong, China taken in 2011 and 2015 were analysed for 6 OPFRs (Ma et al., 2016). Median concentrations of TnBP in these samples were 85.9 ng/g lw in 2011 and 61.7 ng/g lw in 2015. Qiao et al. (2016) analysed human hair and serum to assess exposure to OPFRs. Samples from 49 volunteer participants from Guangzhou, China were taken in 2014. Levels of TnBP in hair was in the range <0.61-25.4 ng/g dw with median 3.3 ng/g dw and a detection frequency of 98%. No TnBP was detected in the serum samples

2.2.9 TPHP/TPP

TPHP has previously been detected in human milk from Sweden, fish from Sweden, China and the Philippines, mussels from Sweden and domestic birds from China (Wei et al., 2015).
Brandsma et al. (2015) determined TPHP in different species from an estuarine food web in the Western Scheldt in the Netherlands. TPHP was detected in cockle, common shore crab, lugworm, placie, goby, sculpin and in zooplankton/jelly fish. Median concentrations were in the range 0.21 (zooplankton/jelly fish)-2 (lugworm) ng/g ww. TPHP was in this study not detected in herring, phytoplankton, pouting nor in common tern eggs.
Herring gull eggs from five different colonial nesting sites taken in the period 1990-2010 from the Laurentian Great Lakes of North America contained TPHP in the range nd-0.81 ng/g ww (Greaves et al., 2016). In the same study, TPHP was only detected in mysis (0.95 ng/g ww) and plankton (0.67 ng/g ww) among the different food web samples (lake trout, rainbow smelt, slimy sculpin, round goby, deepwater sculpin, alewife, mysis, net plankton, herring gull eggs, walleye, emerald shiner, trout perch, yellow perch, white perch and freshwater drum) collected in 2010. Hallanger et al. (2015) screened eight arctic species for 14 OPFRs. TPHP was detected in capelin (whole body, range: 15.8-78.6 ng/g lw), only two of ten harbor seals (plasma, nd-15.3 ng/g lw) and in only one of twenty polar bears (plasma, 5.36 ng/g lw). In liver from kittiwake, eggs from Brünnich's guillemot (n=10) and glaucous gulls (n=12), blubber from ringed seals (n=10) and liver from arctic fox (n=10) TPHP was below the detection limit. Malarvannan et al. (2015) investigated the levels, profiles and human health risk of organophosphorus flame retardants and plasticizers (PFRs) in wild European eels from fresh water bodies in the highly populated and industrial Flanders region (Belgium). In this study the median value for total OPFRs in muscle for the 26 sites investigated was 44 ng/g lw (8.4 ng/g ww), whereof TPHP constituted only 17%. Muscle tissues from Nile tilapia from an e-waste processing area in northern Vietnam was analysed for both monomeric and oligomeric OPFRs. Concentration range for TPHP was 43-230 ng/g lw with median of 92 ng/g lw (n=15) (Matsukami et al., 2016). TPHP was detected in less than 50% of the chicken egg samples taken from an e-waste recycling region in China (Zheng et al., 2016). Concentration ranges and detection frequencies for the four different sites studied were <0.23-0.69 (50%), <0.23-0.36 (43%), <0.23-0.43 (40%) and <0.23-0.29 (25%) ng/g ww (the latter being the control site).
Several recent studies have looked into the exposure of humans to OPFRs. Ding et al. (2016) determined 12 OPEs in human placenta collected in Eastern China. TPHP in these samples had a median concentration of 15.1 ng/g lw, range nd-112 ng/g lw and a detection frequency of 86%. Pooled human serum samples from residents of Shandong, China taken in 2011 and 2015 were analysed for 6 OPFRs (Ma et al., 2016). Median concentrations of TPHP in these samples were 33.2 ng/g lw in 2011 and 29.7 ng/g lw in 2015. Qiao et al. (2016) analysed human hair and serum to assess exposure to OPFRs. Samples from 49 volunteer

participants from Guangzhou, China were taken in 2014. Levels of TPHP in hair was in the range <1.43-352 ng/g dw with median 20.5 ng/g dw and a detection frequency of 84%. No TPHP was detected in the serum samples. OPFRs were also investigated in 50 rice samples, 75 commonly consumed foods and 45 human hair samples from China (Zhang et al., 2016). Median concentration for TPHP in rice (n=50) was 1.29 ng/g (range: nd-111, detection frequency: 98%). In various food items (beverages, dairy products, grains, vegetables, meat and fruits) median concentration of TPHP was in the range 0.02 ng/g (meat)-38.8 ng/mL (dairy products) with various detection frequencies ranging from 61% (beverages) to 100% (grains and fruits). In the human hair samples the median concentration of TPHP was 3.24 ng/g dw (range: 0.18-40.9 ng/g dw, detection frequency: 100%).

2.2.10 TEHP

TEHP has previously been detected in fish from China and the Philippines and domestic birds from China (Wei et al., 2015).

Brandsma et al. (2015) determined TEHP in different species from an estuarine food web in the Western Scheldt in the Netherlands. TEHP was detected in cockle, phytoplankton, zooplankton/jelly fish and in 1 of 5 samples of pouting. Median concentrations were all below 0.06 (cockle)-2.6 (phytoplankton) ng/g ww. TEHP was in this study not detected in common shore crab, lugworm, sole, plaice, goby, sculpin, herring nor in common tern eggs.

TEHP was not detected in any of the herring gull eggs taken from five different colonial nesting sites in the period 1990-2010 from the Laurentian Great Lakes of North America (Greaves et al., 2016). Nor in the different food web samples (lake trout, rainbow smelt, slimy sculpin, round goby, deepwater sculpin, alewife, mysis, net plankton, herring gull eggs, walleye, emerald shiner, trout perch, yellow perch, white perch and freshwater drum) collected in 2010 in the same study was TEHP detected. Hallanger et al. (2015) screened eight arctic species for 14 OPFRs. TEHP was detected in two of ten capelins (whole body, range: nd-26.4 ng/g lw), in two of ten kittiwakes (liver, range: nd-8.86 ng/g lw), one of ten Brünnich's guillemots (egg, 7.1 ng/g lw), two of twelve glaucous gulls (egg, nd-6.79 ng/g lw), two of ten ringed seals (blubber, nd-3.16 ng/g lw) and in arctic fox (liver, nd-8.75 ng/g lw). In plasma from harbour seals (n=10) and polar bears (n=20) TEHP was below the detection limit. TEHP was not detected in any of the chicken egg samples taken from an e-waste recycling region in China (Zheng et al., 2016).

Several recent studies have looked into the exposure of humans to OPFRs. Ding et al. (2016) determined 12 OPEs in human placenta collected in Eastern China. TEHP in these samples were in the concentration range nd-53.5 ng/g lw and had a detection frequency of only 8%. Qiao et al. (2016) analysed human hair and serum to assess exposure to OPFRs. Samples from 49 volunteer participants from Guangzhou, China were taken in 2014. Levels of TEHP in hair was in the range <0.05-151 ng/g dw with median 24.1 ng/g dw and a detection frequency of 98%. No TEHP was detected in the serum samples. OPFRs were also investigated in 50 rice samples, 75 commonly consumed foods and 45 human hair samples from China (Zhang et al., 2016). Median concentration for TEHP in rice (n=50) was 3.33 ng/g (range: nd-72, detection frequency: 98%). In various food items (beverages, dairy products, grains, vegetables, meat and fruits) median concentration of TEHP was in the range 0.02 ng/g (meat)-197 ng/mL (beverages) with detection frequencies of 80-100%. In the human hair samples the median concentration of TEHP was 1.41 ng/g dw (range: 0.21-15.2 ng/g dw, detection frequency: 100%).

2.2.11 TBPP/TTBPP

No recent data on levels of TBPP in biota has been found.

2.2.12 BPDPP/tBPdPP

No recent data on levels of BPDPP in biota has been found.

2.2.13 bBPPP

No recent data on levels on BPPP in biota has been found.

2.2.14 TEP

TEP has previously been detected in fish from China and the Philippines (Wei et al., 2015).
Several recent studies have looked into the exposure of humans to OPFRs. Ding et al. (2016) determined 12 OPEs in human placenta collected in Eastern China. TEP in these samples had a median concentration of 10.2 ng/g lw, range nd-76.4 ng/g lw and a detection frequency of 92%. Qiao et al. (2016) analysed human hair and serum to assess exposure to OPFRs. Samples from 49 volunteer participants from Guangzhou, China were taken in 2014. Levels of TEP in hair was in the range <48-3.84 ng/g dw with median 0.3 ng/g dw and a detection frequency of 51%. No TEP was detected in the serum samples.

2.2.15 BDPP/DPhBP

Hallanger et al. (2015) screened eight arctic species for 14 OPFRs. DPhBP was detected in only one of ten capelins (whole body, 9.85 ng/g lw) and in one of ten arctic foxes (liver, 0.67 ng/g lw). In liver from kittiwake, eggs from Brünnich's guillemot (n=10) and glaucous gulls (n=12), blubber from ringed seals (n=10), liver from arctic fox (n=10) and plasma from polar bears (n=20) TPHP was below the detection limit.

2.2.16 DBPP/DBPHP

Hallanger et al. (2015) screened eight arctic species for 14 OPFRs. In all these samples DBPHP was below the instrument LOD.

2.2.17 TXP/TDMPP

Muscle tissues from Nile tilapia from an e-waste processing area in northern Vietnam was analysed for both monomeric and oligomeric OPFRs. Concentration range for TDMPP was <5-7.9 ng/g lw with detection frequency of only 7% (n=15) (Matsukami et al., 2016).

2.2.18 IPP

No recent data on the presence of IPP in biota has been found.

In summary chlorinated OPFRs are found in biota but by far not in all samples and with no clear pattern, in some cases a significant background of especially for TCPP. For all OPFRs most data is available for the chlorinated OPFRs and they are often found in the lower end of the food chain (polychaetes, mussels, krill and prawns) but also occasionally in herring and fish liver (flounder) in Nordic samples (Miljödirectoratet 2016). For the other OPFRs the detection frequency is much lower and for some of the compounds not recent data is available. Surprisingly the carboxylate OPFR, TBOEP was not only found in herring muscle from Norway but also in nearly all cod liver samples (9/16), together with TPP (4/15) (Miljødirektorat 2016), herring gull blood (13/15) (Miljødirektorat 2015) and in herring gull eggs and flounder liver (Miljødirektorat 2014). Several aromatic OPFRs were occasionally found with the highest detection rates for TTP in both fish fillet (41/46), bird liver and egg.

2.3 Metabolites of OPFRs

Cequier et al. 2015 determined levels of different metabolites of some of the compounds discussed in this report in human urine samples from mother-toddler pairs and in air and dust from their households. These studies showed significant correlation between children urinary levels of diphenyl phosphate (DPHP) and

bis(1,3-dichloro-2-propyl) phosphate (BDCIPP) and levels of the parent compounds TPHP and TDCIPP in air and dust. Median urinary concentrations of diphenyl phosphate (DPHP) were 1.1 and 0.51 ng/mL in children and mothers, respectively, followed by bis(1,3-dichloro-2-propyl) phosphate (BDCIPP) with medians of 0.23 and 0.12 ng/mL, respectively. Low detection frequencies for bis(2-butoxyethyl) phosphate (BBOEP) in urine from children and mothers were observed (32 and 1%, respectively, median <0.18 ng/mL), and for di-n-butyl phosphate (DNBP; 15 and 8%, respectively, median <0.12 ng/mL). For mothers, only the urinary concentration of BDCIPP was correlated to its precursor in dust from the households (R_S=0.40; p<0.01). This might indicate higher impact of the household environment on children than mothers. In contrast, no relevant associations between OPFR metabolites in urine and food consumption data were seen. This suggests that the indoor environment is a more important exposure pathway to OPFRs than the diet.

Butt et al. 2016 examined urinary levels of PFR metabolites and TBBA in 28 mother-child pairs from California, USA, collected in 2015. BDCIPP, DPHP, ip-PPP and BCIPHIPP conjugates were detected in 100% of the mother and child urine samples. Concentrations in mothers (n=28) were in the ranges 0.98-14.3 ng/mL, 0.39-3.5 ng/mL, 0.56-14.8 ng/mL and 0.42-104 ng/mL, respectively. Concentrations in children (n=33) were in the ranges 1.7-798 ng/mL, 0.36-82 ng/mL, 0.44-8.5 ng/mL and 0.37-23.2 ng/mL, respectively.

The metabolites DPHP, ip-DPHP, tb-DPHP, BDCIPP and BCIPP was found in urine from infants from the US (Hoffman et al., 2015). BDCIPP was detected in all 43 urine samples with median concentration of 7.3 ng/mL and range 0.8-541 ng/mL. DPHP was detected in 93% of the urine samples with median concentration of 3.2 ng/mL and range <0.22-26.5 ng/mL. ip-DPHP, BCIPP and tb-DPHP had detection frequencies of 35%, 19% and 4.7%, and concentration ranges of <0.07-6.1 ng/mL, <0.02-7.5 ng/mL and <0.03-0.5 ng/mL, respectively.

Petropoulou et al. (2016) analysed 13 adult California urine samples for four di-ester metabolites. BCEP was detected at 0.4–15 ng/mL with a geometric mean of 1.9 ng/mL; BDCIPP at 0.5–7.3 ng/mL, (GM: 2.5 ng/mL) and DPhP at <0.2-5.6 ng/mL, (GM: 1.7 ng/mL). BCIPP was detected in 92.3% of the samples with two to three times lower values (range <0.04-3.5 ng/mL and GM: 0.4 ng/mL) than the other OPFRs. Su et al. (2016) determined glucuronide conjugates of OH-TPHP in 13 human urine samples from four volunteers from Ottawa, Canada. *p*- and *m*-OH-TPHP glucuronides were detectable in 13 and 9 of the samples, at concentrations ranging from <MLOQ-25 pg/mL and nd-4 pg/mL, respectively. A strong, positive correlation was observed between *p*-OH-TPHP glucuronide and DPHP concentrations. Herein suggested that *p*-OH-TPHP glucuronide measured in urine is likely the best possible biomarker of TPHP exposure in humans.

A total of 95 pooled human urine samples from Taringa, QLD, Australia were analysed for nine OPFR metabolites (OH-TPHP, DPHP, DBP, BDCIPP, BCEP, BCIPHIPP, BCIPP, OH-TBOEP and BBOEP) (van den Eede et al., 2015). Levels of DPHP were in the range <0.30-727 ng/mL with a detection frequency of 97%. Levels of BDCIPP were in the range <0.15-8.9 ng/mL with a detection frequency of 92%. Levels of BCIPHIPP were in the range 0.37-9.43 ng/mL with a detection frequency of 100%. Levels for DBP and BBOEP were in the ranges <0.43-0.94 and <0.35-0.53 with detection frequencies of 18% and 6%, respectively. OH-TBOEP and OH-TPHP were not detected in any samples.

3 Toxicity

Information on toxicity of selected OPFRs was compiled by searching the recent peer reviewed literature from 2015 to 2016. Initially, it was planned to use SciRap for scoring the papers based on reliability and relevance of the study. However, due to the high number of relevant studies (>30), limited time and budget, and a SciRap training event occurring after the report deliverance, it was decided to use expert judgement at this stage. Also, SciRap is mainly used for scoring reliability and relevance of studies used in risk assessment. Relevant papers have been selected based on expert judgement to cover effects relevant for assessment of the T criteria. All included studies are from peer review literature which guarantee a certain level of reliability. This report will focus on eco toxicological effects although a few studies related to human and mammalian toxicity have been included due to limited number of studies.

Acute and chronic effects were compiled from the ECHA registration dossiers (https://echa.europa.eu/information-on-chemicals/registered-substances) by search for cas numbers. Toxicity data for algae, aquatic invertebrates (long term NOEC and short term EC50) and fish (long term NOEC and short term EC50) were prioritized for compilation. Values determined by QSAR was not included and due to limited data, all available data were included independent on the reliability of the study indicated by ECHA. For several of the selected OPFRs, no results were found by search on the cas number.

3.1 TCEP

In an assessment update on alternative flame retardants by US EPA, TCEP was assessed to have high hazard on the following human health effects; acute toxicity, carcinogenicity and development, moderate hazard on the endpoints genotoxicity, reproductive, neurological and repeated dose, and low hazard on for skin sensitization, eye irritation and dermal irritation. For aquatic toxicity, high hazard was noted for both acute and chronic toxicity (US EPA, 2015).

Aquatic toxicity data reported by ECHA showed that the substance appeared to affect the growth of algae with a NOEC of ~72 mg/L and an EC50 of 450 mg/L (ECHA). The short term EC50 for aquatic invertebrates was reported as ~170 mg/L (ECHA), and a recent study found the 96h LC50 in zebrafish embryo test (performed according to the OECD guideline No. 236, 2013) to be 202 mg/L (Du et al., 2015). In a test with zebrafish early life stage, a 120hpf (hours post fertilization) lowest effect level for mortality was reported at 0.0064µM (Noyes et al., 2015).

Only one study investigating endocrine disruption of TCEP in fish have recently been published. In this study, *in vivo* exposure to TCEP (0.04, 0.2 and 1 mg/L) affected several genes involved in the steroidogenesis in juvenile Atlantic salmon (Salmo salar) (Arukwe et al., 2016).

Two studies on rodents (*in vivo* and *in vitro*) were available in recent literature. Two studies showed and supported endocrine disruption in male mice where a reduction in the number of leydig cells, sertoli cells and spermatogenic cells were observed in mice exposed to 100 mg/kg and 300mg/kg. In addition, absolute disintegration of seminiferous tubule structure and reduced testicular testosterone (T) concentrations was observed in mice exposed to 300 mg/kg. These effects were supported by altered expression of genes involved in T synthesis (Chen et al., 2015a), which was also observe *in vitro* in TM3 Leydig cells (Chen et al., 2015b).

Endocrine effects related to the thyroid were observed in adult male American kestrels (Falco sparverius) fed 22 ng TCEP/g kestrel/d) daily for 21 d. The exposure resulted in significant effects on plasma free triiodothyronine (FT3) concentrations and overall effects on free thyroxine (FT4) (Fernie et al., 2015).

A review of the neurotoxic potential of alternative flame retardants was performed by Hendriks and Westerink (Hendriks and Westerink, 2015). The overall neurotoxic potential was derived from the highest *in vitro*, zebrafish and/or *in vivo* neurotoxic potential and findings on acetylcholinesterase (AChE) and

neuropathy target esterase (NTE, both major targets for organophosphates). TCEP was assessed to have low neurotoxic potential (Hendriks and Westerink, 2015). However, developmental effects were observed in the embryo test with Japanese medaka (*Oryzias latipes*) exposed to TCEP, where significant effect on body length was observed at 1250 µg/L (Sun et al., 2016a), and a 96h EC_{50} of pericardium edema in the zebrafish embryo test was observed at 179 mg/L (Du et al., 2015). In addition, TCEP significantly affected the average speed of the larvae and affected expression of genes related to the nervous system in the zebrafish embryo test (Sun et al., 2016b). Whereas an *in vivo* study with rats exposed to TCEP did not support the potential for developmental neurotoxicity of this compound (Moser et al., 2015).

An *in vivo* study investigating growth effects and effects on the oxidative stress in male mice after exposure to TCEP found that TCEP-treatments decreased the body weights and testes weights of the mice. Exposure of TCEP also resulted in reduced liver weights. Oxidative stress as indicated by reduced GSH content in the liver, increased activity of antioxidant enzymes SOD, CAT and GPX in the liver and decreased activity of GST was observed. Generally, the transcriptional patterns of Sod1, Sod2, Gpx1, Gpx2and Cat in response to TCEP treatments were similar to the change in the activities of their respective enzymes (Chen et al., 2015a). Similar results were obtained *in vitro* with TM3 Lydig cells where significant increases in superoxide dismutase (SOD), catalase(CAT), glutathione peroxidase (GPX) and glutathione S-transferase (GST) activities and their respective gene expression occurred in a dose-dependent and/or time-dependent manner in TCEP exposed cells (Chen et al., 2015b).

TCEP in not classified as PBT/vPvB according to ECHA. However, US EPA (2015) denotes high hazard for acute and chronic aquatic toxicity, and high hazard related to several human health effects. One recent study reported an EC_{50} for mortality in the zebrafish embryo test at 0.0064 µM (0.0018 mg/L) which is below the screening criteria for T. The recent literature also indicates that the substance has potential for endocrine disruptive and neurotoxic and developmental effects at higher concentrations.

3.2 TCPP/TCIPP

A recent report on Environmental and health screening pro-files of phosphorous flame retardants (Lassen et al., 2016) evaluated TCPP to have high hazard on the human health effects; reproductive toxicity and developmental toxicity, moderate hazard on carcinogenicity, endocrine activity, systemic toxicity and neurotoxicity, and low hazard for mutagenicity, acute mammalian toxicity, skin sensitization, skin irritation and eye irritation. For aquatic acute and chronic toxicity, TCPP pose a moderate hazard (based on data from US EPA 2014a, 2014b, 2015 and summarized in Lassen et al., 2016).

No experimental information on this compound were found in the ECHA data base. However, a study by Du et al (2015) reported the 96h LC_{50} for zebrafish embryo to be 13.5 mg/L, which is above the screening criteria for toxicity.

Only two studies investigating the endocrine effects of TCPP were available in the recent literature. An *in vitro* study using gene reporter assay found that several OPFRs, including TCPP activated PXR agonistic activity with a 20% relative effect concentration lower than $1x10^5$ M (Kojima et al., 2016).
As with TCEP, TCPP were administered to adult male American kestrels, and significant effects on plasma free triiodothyronine (FT3) concentrations were observed (Fernie et al., 2015).

TCPP were assessed to have low neurotoxic potential in the review by Hendriks and Westerink (2015). Only one recent publication was found that investigates the developmental and/or neurotoxic potential of this compound. In this *in vivo* study, the 96h EC_{50} of pericardial edema in zebrafish embryo assay was found to be 22.8 mg/L (Du et al., 2015).

Calculated PNECs for TCPP are 0.42 mg/L (af=10) for freshwater and marine water (ECHA). The data for TCPP is limited, and although the toxicity data is above the T criteria, there is evidence of potential endocrine disruptive, developmental and neurotoxic effects at higher mg/L concentrations.

3.3 TDCPP/TDCIPP

In an assessment update on alternative flame retardants by US EPA (2015), TDCPP was assessed to have high hazard for the human health effects; carcinogenicity, reproductive and repeated dose, Moderate hazard for genotoxicity and development and low hazard for acute toxicity, nerological, skin sensitisation, eye irritation and dermal irritation. High hazard was denoted for acute and chronic aquatic toxicity (US EPA, 2015).

From the registration dossier (ECHA), the NOEC and EC50 for algae toxicity were reported to be 6 mg/L and 12 mg/L, respectively. The short term EC50 for fish was reported as 1.4 mg/L (ECHA), and as 0.418 mg/L (96h) in the zebrafish embryo test (Du et al., 2015). A study with the zebrafish early life stage reported the 120hpf lowest effect level for mortality to be 64 μM (27.6 mg/L) (Noyes et al., 2015).

Several in vitro and in vivo studies investigating endocrine effects of TCDPP were recently published.
For fish, endocrine disruption and impaired reproduction has been observed after long-term in vivo exposure of zebrafish to low concentrations of TDCPP (0, 4, 20 and 100 μg/L) as indicated by increased plasma estradiol and testosterone levels in females, significant reduction in fecundity as indicated by decreased egg production, reduced egg diameter and an increased malformation rate in the F1 generation following TDCPP exposure. Furthermore, hepatic vitellogenin (vtg1 and vtg3) expression was upregulated in both females and males, suggesting TDCPP has estrogenic activity and that long-term exposure to low concentrations of TCDPP leads to impaired reproduction in fish (Wang et al., 2015a). A statistically significant reduction in number of eggs was also observed in zebrafish exposed to 6.30 ± 0.13 μg/L TDCIPP (Zhu et al., 2015). Exposure to TDCPP significantly reduced plasma thyroxine (T4) and 3,5,3-triiodothyronine (T3) levels in female zebrafish (Xu et al., 2015). It has also been shown that TDCPP can be transferred to the offspring of exposed adults causing thyroid disruption and developmental neurotoxicity (Wang et al., 2015b). Effects on reproduction was also observed after exposing the nematode C. elegans to this compound with a lowest effective concentration of 130 μM (Behl et al., 2016).
Endocrine disruption was also observed in male American kestrels fed the (22 ng TDCPP/g kestrel/d) daily for 21 d shown by significant effects on plasma free triiodothyronine (FT3) concentrations and total thyroxine (TT4)(Fernie et al., 2015). However, exposure of rats to TDCPP did not support the potential for thyrotoxicity (Moser et al., 2015).
Two in vitro studies found that TDCPP showed PXR agonistic activity in a gene reporter assay with a 20% relative effect concentration lower than 1x105 M (Kojima et al., 2016) and alterations in the level of AR-induced gene and protein expression in human prostate cancer cell line, indicative of anti-androgenic effects (Reers et al., 2016).

TDCIPP have a high neurotoxic potential (Hendriks and Westerink, 2015), and several recent in vivo studies show developmental and neurotoxic effects of this compound. Developmental exposure of zebrafish larvae to TDCIPP (0.03 and 0.3 μM) induced behavioral changes across the lifespan (Oliveri et al., 2015). It was also shown that developmental exposures to TDCIPP at levels equimolar to those of the known neurotoxicant chlorpyrifos, produce behavioral abnormalities across a number of locomotor and cognitive endpoints in both larval and adult zebrafish (Oliveri et al., 2015). On the molecular level, a reduction in expression of neurotrophic factor genes was observed in Chinese rare minnow after exposure to 200μg/L TDCPP (Yuan et al., 2016). It has been shown that TDCPP can be transferred to the offspring of exposed adults causing developmental neurotoxicity (Wang et al., 2015b). Other developmental effects observed in zebrafish embryo includes pericardial edema (96h EC50 = 1.65 mg/L) (Du et al., 2015), neurodevelopmental effects on the caudal fin (120hpf lowest effect level = 64 μM) (Noyes et al., 2015), development overall (point of departure, POD = 8,9μM) (Behl et al., 2015). Zebrafish embryos (2 h post-fertilization) exposed to TDCPP (0–100 g/L) for 6 months up until sexual maturation showed reductions of dopamine and serotonin levels in the brains of adult females but not males. In addition, downregulation of nervous system development genes was observed in both the male and female brain tissues (Wang et al., 2015c).

Also, the larval development of C. elegans had a POD of 9.8 μM (Behl et al., 2015), and a lowest effective concentration of 13 μM (Behl et al., 2016). The activity in mouse stem cell differentiation showed a POD of 44.1μM (Behl et al., 2015).

A study where white leghorn chicken eggs were injected with TDCIPP concentrations (0, 10, 100, 1000, 50,000 ng/g) at incubation day 0 and exposing embryos throughout the ~21-day in ovo period showed some possible neurodevelopmental effects occurring in a few of the exposure groups and not necessarily in a concentration dependent manner. Observed effects of exposed chicks included higher early-incubation mortality, lower (and higher) maximum velocity in the open field test than vehicle-exposed controls, reduced righting response success. In addition, TDCIPP-exposed chicks had reduced number of degenerate Purkinje cells (at 1000 ng/g), possibly indicating disruption of neurodevelopment (Bradley et al., 2015). Exposure of rats to TDCIPP did not support the potential for developmental neurotoxicity produced by TDCIPP (Moser et al., 2015).
Long-term exposure (6 months) to TDCPP significantly induced the phase I metabolic enzymes 7-ethoxyresorufin O-deethylase (EROD) and 7-methoxyresorufin O-demethylase (MROD) in zebrafish. The mRNA expression of genes related to Phase I and II metabolic enzymes, were also significantly upregulated in exposed fish (Xu et al., 2015).

The substance is not PBT/vPvB according to ECHA. The calculated PNEC for freshwater is 0.01 (af=50) and PNEC marine waters is 0.001 mg/L (af= 500) (ECHA). The recent literature show that the substance has potential for endocrine disruptive and neurodevelopmental effects, although more studies are warranted to make a proper assessment of whether the substance fulfill the criteria for T based on endocrine disruption.

3.4 TBEP/TBOEP

The reported toxicity toward algae of TBEP/TBOEP was a NOEC of 7.6 mg/L and an EC50 of 33 mg/L (ECHA). The toxicity towards aquatic invertebrates was reported to be 75 mg/L in a short term test with aquatic invertebrates (ECHA). The 48h LC50 for Daphnia magna was 147 mg/L (Giraudo et al., 2015). A EC50 of 32 mg/L were reported for fish short term test (ECHA) and a 96h EC50 of 3.34 mg/L was obtained in the zebrafish embryo test (Du et al., 2015). An even lower LC50 of 0.289 mg/L was observed in the early life stage of zebrafish at 96 hpf and 120 hpf (Ma et al., 2016), and a 120 hpf lowest effect level of 6.4 μM (2.55 mg/L) was obtained by Noyes et al (2015). The predicted no effect concentration (PNOEC) in the early life stage of zebrafish was 0.0024 mg/L (Ma et al., 2016).

In vivo experimental studies using fish, crustacean and birds were available in the recent published literature, in addition to one *in vitro* study. The studies show effects on reproduction and the endocrine systems. A study by Kwon et al. (2016) showed that exposure of adult zebrafish to TBOEP led to decrease in egg production and lowered hatching rate (at 118 μg/L) (Kwon et al., 2016). In addition, Ma et al (2016) found that exposure to 0.5 mol/L TBOEP on early life stages of zebrafish significantly up-regulated expression of estrogen receptor (ER) genes and ER-associated genes, indicating that TBOEP modulates the ER pathway (Ma et al., 2015). However, TBOEP did not significantly affect the expression of steroidogenesis related genes in juvenile Atlantic salmon (Arukwe et al., 2016).
A study with Daphnia magna showed that chronic exposure (21 d) to a range of sublethal concentrations of TBOEP (14.7–1470 μg/L) did not impact growth, survival or reproduction, but the number of offspring decreased between the lowest and the highest dose. The total number of neonates produced was not different from unexposed controls but was however significantly lower at 1470 μg/L compared to 14.7 μg/L. In addition, the exposure impacted gene transcription related to proteolysis, protein synthesis, and energy metabolism (Giraudo et al., 2015).

Thyroid disruption was observed in adult male American kestrels as indicated by significant effects on plasma free triiodothyronine (FT3) concentrations and overall effects on free thyroxine (FT4) (Fernie et al., 2015).

A gene reporter study found that TBOEP showed PXR agonistic activity with a 20% relative effect concentration lower than 1x105 M (Kojima et al., 2016).

TBEP was classified as having low neurotoxic potential by Hendriks and Westerink (2015). Several *in vivo* fish studies were available in the recent literature showing developmental and neurotoxic effects. Developmental malformations were observed in zebrafish exposed to 2000 µg/L TBOEP for 72 hpf (curvature of the spine) and 5000 µg/L TBOEP until 120 hpf (edemas) (Ma et al., 2016). In addition, delayed hatching was observed and larvae that survived exposure to 5000 µg/L were significantly shorter than control fish (Ma et al., 2016). TBOEP exposure resulted in significant effect on hatchability (6250 µg/L), time to hatch (6250 µg/L), gross abnormality rate (6250 µg/L), heart rate (1250 µg/L), and body length (1250 µg/L) in Japanese medaka. (Sun et al., 2016a). The 96h EC50 for pericardial edema in the zebrafish embryo test was 4.10 mg/L (Du et al., 2015), and the lowest effect level for yolc sac edema was 6.4E-4µM (Noyes et al., 2015). A study using the zebrafish embryo test found that exposure to TBOEP significantly affected the average speed of the larvae and affected expression of genes related to the nervous system (Sun et al., 2016b).

According to ECHA, the compound is not PBT/vPvB, and the acute toxicity is between 10 and 100 mg/L for all species (ECHA). The calculated PNEC for freshwater is 24 µg/L (af = 1000) and for marine waters the PNEC is 2.4 µg/L (af 10 000) (ECHA). However, some evidence for endocrine disruption was available in recent literature.

3.5 EHDPP/EHDPHP

EHDPP appear to be the most toxic of the investigated OPFRs with a NOEC and EC50 for algae toxicity of 0.03 mg/L and 0.2 mg/L respectively (ECHA). The reported NOEC for long term test with was 0.18 mg/L for aquatic invertebrates and 0.021-0.058 for fish, whereas the short term EC50 for fish was >0.38 mg/L (ECHA). The 120 hpf lowest effect level for mortality in the zebrafish early life stage was 64 µM (23.2 mg/L) (Noyes et al., 2015).

The neurotoxic potential of EHDPP was assessed to be low (Hendriks and Westerink, 2015). Only two studies investigating the neurotoxic and developmental effects of EHDPP were found and included from the recent literature. A study using zebra fish embryo found that EHDPP affected the Axes development and induced pericardial edemas with a 120 hpf lowest effect level of 64 µM (Noyes et al., 2015). Developmental toxicity was also observed in C. elegans where the point of departure from normal larval development was 2.3 µM (0.83 mg/L) (Behl et al., 2015) and the lowest effective concentration was 1.60 µM (0.58 mg/L) (Behl et al., 2016). For the zebrafish embryo development, the POD was 15.3 µM (Behl et al., 2015). Developmental neurotoxicity was investigated with *in vitro* assays and the POD for neuroprogenitor proliferation in human neuroprogenitor (hNP1) cells was 13.2µM and the POD for humane neurite outgrowth in human neurons (hN2) cells was 6.9µM (Behl et al., 2015).

The available data for the substance EHDPP in the ECHA data base does not fulfill the T criteria for toxicity. However, no assessments of endocrine disrupting properties were found and there are some indications of developmental effects reported in recent literature. Thus more information is warranted to assess whether or not this compound might fulfil the T criteria.

3.6 TCP/TMPP/TCrP

A recent report on Environmental and health screening profiles of phosphorous flame retardants (Lassen et al., 2016) evaluated TCP to have high hazard for the human health effects; reproductive toxicity and

systemic toxicity, moderate hazard for developmental toxicity, acute mammalian toxicity, neurotoxicity and skin sensitization, and low hazard for carcinogenicity, mutagenicity, skin irritation, and eye irritation. Very high hazard for acute aquatic toxicity and high hazard for chronic aquatic toxicity was proposed (based on data from US EPA 2014a, 2014b, 2015 and summarized in Lassen et al., 2016).

No results on the ECHA registered substances page was found when searching for this compounds cas number. The 24 hpf and 120 hpf lowest effect level for mortality on the early life stage of zebrafish was 0.0064 μM (0.002 mg/L) (Noyes et al., 2015).

Only one study was found and included from the recent literature investigating neurodevelopmental effects. Exposure of zebrafish embryo to TCP resulted in yolc sac edemas, alterations of the developmental axis, pericardial edema and alterations in touch responses (all with lowest effect level = 64 μM = 24 mg/L) (Noyes et al., 2015). Larval development in the nematode C. elegans was also affected by TMPP with a lowest effective concentration of 100 μM (Behl et al., 2016).

The reported values for toxicity (lowest effect level of 0.002 mg/L) appear to fulfil the T criteria. This is supported by the evaluation and summarization in Lassen et al (2016), stating very high hazard for acute aquatic toxicity.

No results on the ECHA registered substances page was found when searching for the cas numbers of the three isomers of TCP (T*o*CP, T*m*CP and T*p*CP). However, a few results in recent literature was found for T*o*CP. The compound was shown to reduce the cell viability at 0.25 mM and induce autophagy in rat spermatogonial stem cells (Liu et al., 2015). The 120 hpf lowest effect level for mortality in zebrafish early life stage was 64 μM (24 mg/L) (Noyes et al., 2015).

The neurotoxic potential of T*o*CP was assessed to be moderate by Hendriks and Westerink (2015).
Due to limited data and no assessment of endocrine effects, whether or not this isomer fulfil the T criteria cannot be assessed. However, the substance was assessed to have moderate neurotoxic potential so further studies on endocrine effects and neurotoxic and developmental effects are warranted.

3.7 CDPhP/CDPP/MPDPP

A recent report on Environmental and health screening profiles of phosphorous flame retardants (Lassen et al., 2016) evaluated CDPhP to have high hazard for the human health effects; reproductive toxicity and systemic toxicity, moderate hazard for developmental toxicity, acute mammalian toxicity, neurotoxicity and skin sensitization, and low hazard for carcinogenicity, mutagenicity, skin irritation, and eye irritation. Very high hazard for acute aquatic toxicity and high hazard for chronic aquatic toxicity was proposed (based on data from US EPA 2014a, 2014b, 2015 and summarized in Lassen et al., 2016).

No results on the ECHA registered substances page was found when searching for this compounds cas number. The 96h LC50 in the zebrafish embryo test was 1.06 mg/L (Du et al., 2015).

The neurotoxic potential of CDPhP was assessed by Hendriks and Westerink (2015) and concluded to be low. An in vivo study using zebrafish embryo found that CDPhP induced cardiotoxicity during zebrafish embryogenesis, probably by disturbing expression of transcriptional regulators (Du et al., 2015). The study showed that the cardiac looping progress could be impeded by 0.10 mg/L CDP exposure. Bradycardia and reduction of myocardium were also observed in 0.10, 0.50, and 1.0 mg/L CDP groups (Du et al., 2015). The 96h EC50 of pericardial edema was 0.38 mg/L, and 0–48 hpf was found to be the most vulnerable developmental window in which cardiomyogenesis and cardiac function could be affected by CDP (Du et al., 2015).

Although limited data for aquatic toxicity was found, the hazard for acute and chronic aquatic effects were evaluated to be very high and high respectively (Lassen et al., 2016). Further studies are warranted to assess

if the substance fulfil the T criteria as no assessment of endocrine effects and only one study looking at developmental effects was found in the recent literature.

3.8 TBP/TnBP

This substance has a harmonised classification according to the CLP Regulations as carcinogenic (Carc. 2) (reported in Lassen et al., 2016).

Toxicity data for aquatic invertebrates and fish were available in the ECHA registration dossiers. The long term NOECs was 1.3 mg/L for aquatic invertebrates and 0.82 for fish (ECHA). The short term EC50s was 68 mg/L for aquatic invertebrates and 11 mg/L for fish (ECHA). The acute toxicity in the zebrafish embryo test showed an 96h LC50 of 7.82 mg/L (Du et al., 2015), and a lowest effect level of 6.4E-4 μM (0.0002 mg/L) was observed for 120 hpf zebrafish larvae (Noyes et al., 2015).

A gene reporter study found that TBP showed PXR agonistic activity and AR and GR antagonistic activity. For all endpoints, the 20% relative effect concentration was lower than 1x105 M (Kojima et al., 2016).

The neurotoxic potential of TBP was assessed to be low (Hendriks and Westerink, 2015). Three studies using zebrafish embryos to assess neurotoxic and developmental effects were found in the recent literature. The studies show that TBP affects the development as shown by pericardial edema with a 96h EC50 of 17.7 mg/L (Du et al., 2015), and a lowest effect level of 0.0064 μM for development of the pectoral fin (Noyes et al., 2015), and alterations in the average speed of exposed larvae and affected expression of genes related to the nervous system (Sun et al., 2016b). Effects on hatchability, gross abnormality rate and heart rate was observed in the embryo test with Japanese medaka (Sun et al., 2016a).

Tributyl phosphate is not classified as PBT/vPvB by ECHA. The PNEC is calculated to 0.082 mg/L with an assessment factor of 10 for freshwater. However, the substance has a harmonised classification according to the CLP Regulations as carcinogenic, and one study showed toxicity at concentrations below the T criteria. In addition, several studies showed developmental effects.

TBP/TiBP

Acute toxicity data for algae, aquatic invertebrates and fish were available from ECHA. The EC50 values were 34.1 mg/L for algae, 5.8 mg/L for aquatic invertebrates and 20 mg/L for fish (ECHA). The neurotoxic potential of TiBP was assessed to be low (Hendriks and Westerink, 2015).

The substance in not classified as PBT/vPvB by ECHA and the calculated PNEC is 0.011 mg/L for freshwater (af = 1000) and 0.001 mg/L for marine water (af = 10 000) (ECHA).

No recent literature was found for this substance and no information on potential endocrine effects was found. Although the available data suggest the substance to not fulfil the T criteria, the lack of information regarding endocrine effects hampers a proper assessment.

3.9 TPP/TPHP

A recent report on Environmental and health screening profiles of phosphorous flame retardants (Lassen et al., 2016) evaluated TPP to have high hazard for the human health effects; endocrine activity and systemic toxicity, moderate hazard for carcinogenicity, and low hazard for mutagenicity, reproductive toxicity, developmental toxicity, acute mammalian toxicity, neurotoxicity, skin sensitization, skin irritation, and eye irritation. Very high hazard for acute and chronic aquatic toxicity was proposed (based on data from US EPA 2014a, 2014b, 2015 and summarized in Lassen et al., 2016).

Toxicity data for TPP was available from ECHA. The NOEC for algae was 2.5 mg/L and for aquatic invertebrates 0.254 mg/L. The EC50 values from short term tests was 0.25 mg/L for aquatic invertebrates and 0.3 for fish (ECHA). The 120 hpf lowest effect level for mortality in zebrafish early life stage was 0.0064 μM (0.002 mg/L) (Noyes et al., 2015), and the LC50 for zebrafish was 1.53 mg/L in the zebrafish embryo test (Du et al., 2015) and 1.026 mg/L for adult zebrafish (Du et al., 2016). The study also showed indications that TPhP induced apoptosis in zebrafish liver, and disruption of metabolism (Du et al., 2016).

In fish, exposure to TPP has shown estrogenic effects (Liu et al., 2016) and effects on thyroid hormones (Kim et al., 2015). Zebra fish larvae exposed until 7 dpf showed significantly increased concentrations of T3 and T4, and up-regulation of genes involved in thyroid hormone synthesis (Kim et al., 2015), whereas zebrafish exposed from 4 hpf to 120 dpf showed effects on proteins and genes involved in the HPG axis as well as induction of estrogenic effects. Some parameters (plasma E2) were affected from concentrations of 5 μg/L (Liu et al., 2016). A study with C. elegans showed that TPHP affected reproduction of the nematodes with a lowest effect concentration of 6.30 μM (2.06 mg/L) (Behl et al., 2016).

An *in vivo* study with male mice showed decreased leydig cells, mild disorganization of Sertoli cells and reduced testicular T concentrations after exposure to 300 mg/kg TPP for 35 days. In addition, expression of main genes related to testosterone synthesis in the testes also decreased after the exposure to 300 mg/kg TPP (Chen et al., 2015a). These findings were supported by an *in vitro* study with TM3 Leydig cells showing significant decreases in T levels and changes in the expression of T synthesis related genes (Chen et al., 2015b). An *in vivo* study investigating growth effects and effects on the oxidative stress in male mice after exposure to TPP found that TPP-treatments decreased the body weights and testes weights of the mice. Oxidative stress as indicated by reduced GSH content in the liver, increased activity of antioxidant enzymes SOD, CAT and GPX in the liver and decreased activity of GST was observed. Generally, the transcriptional patterns of Sod1, Sod2, Gpx1, Gpx2and Cat in response to TPP treatments were similar to the change in the activities of their respective enzymes (Chen et al., 2015a). Similar results were obtained in vitro with TM3 Lydig cells where significant increases in superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPX) and glutathione S-transferase (GST) activities and their respective gene expression occurred in a dose-dependent and/or time-dependent manner in TPP exposed cells (Chen et al., 2015b).

A gene reporter study found that TPP showed PXR agonistic activity and ERα and ERβ, AR and GR agonistic activity. For all endpoints, the 20% relative effect concentration was lower than 1x105 M (Kojima et al., 2016).

The neurotoxic potential of TPP was assessed to be moderate (Hendriks and Westerink, 2015). Several *in vitro* and *in vivo* studies from recent literature have shown that TPP affects the development and developmental neurotoxicity *in vivo* and/or *in vitro*. Several developmental effects have been observed in zebrafish embryo, including yolc sac edema (120 hpf lowest effect level of 64 μM, 21mg/L) (Noyes et al., 2015), pericardial edema (96h EC50 of 0.64 mg/L) (Du et al., 2015), behavioral changes across the lifespan (from zebrafish larvae exposed to 0.03 and 0.3 μM = 0.0098 and 0.098 mg/L) (Oliveri et al., 2015). The POD for zebrafish embryo development was observed at 2 μM (0.65 mg/L) (Behl et al., 2015). It was also found that the cardiac looping progress could be impeded by 0.10 mg/L TPhP exposure. Bradycardia and reduction of myocardium were observed in 0.50 and 1.0 mg/L TPhP groups, and 0–48 hpf was concluded to be the most vulnerable developmental window in which cardiomyogenesis and cardiac function could be affected by TPhP (Du et al., 2015). It has been suggested that zebrafish retinoic acid receptors may be involved in mediating TPP-induced developmental toxicity (Isales et al., 2015). Developmental effects were also observed in embryo test with japanese medaka where significant effect on hatchability (625 μg/L), time to hatch (625 μg/L), gross abnormality rate (625 μg/L), heart rate (125 μg/L) and body length (125 μg/L) were observed (Sun et al., 2016a). In addition, the development of C. elegans larvae was affected at 0.9 μM (0.29 mg/L) TPP (Behl et al., 2015), and a lowest effective concentration of 0.16 μM (0.05 mg/L) was obtained in a later study (Behl et al., 2016).

In vitro assessment of developmental neurotoxicity showed that TPP could reduce the neurite outgrowth of human neurons (hN2) cells with a POD of 15.9 μM (Behl et al., 2015). It has also been shown that DNA

damage repair and cell cycle pathways, including DNA replication, cell cycle, non-homologous end-joining (NHEJ) and base excision repair (BER) pathways, were strongly affected (hampered) in adult zebrafish after exposure to TPHP (Du et al., 2016).

Exposure of zebrafish for 7 days to 0.050 and 0.300 TPhP mg/L followed by metabolomic analysis resulted in 19 significantly changed metabolites which were indicative of induced metabolic disruption in the zebrafish liver. The metabolites were involved in carbohydrate metabolism (glucose, UDP-glucose, glycolate, fumarate, succinate, and lactate), lipid and fatty acid metabolism (choline, acetylcarnitine, esterified cholesterol, arachidonic acid [ARA], timnodonic acid [EPA], linoleic acid and fatty acids identified by α H2), amino acid metabolism (glutamate, glutamine and leucine), and osmolyte metabolism (TMAO, dimethylamine [DMA]). It was also observed that TPhP had comprehensive toxic effects in zebrafish liver after a one-week exposure period even at the low dose (0.050mg/L) (Du et al., 2016).

The substance is not PBT according to ECHA, and the PNEC for freshwater is 0.004 mg/L (af = 10) (ECHA). The available literature suggests that the substance might have the potential to induce a number of effects at higher concentrations. However, one study reported a lowest effect level for mortality in zebrafish early life stage to be 0.0064 μM (0.002 mg/L) which fulfils the T criteria. This is supported by the denotation of very high hazard for acute and chronic aquatic toxicity in Lassen et al. (2016).

3.10 TEHP

The toxicity of TEHP was reported as > 40 mg/L for algae (long term NOEC and short term EC50), 1 mg/L (long term NOEC) and >0.08 mg/L (short term EC50) for aquatic invertebrates, and > 100 for short term EC50 in fish (ECHA). The 120 hpf lowest effect level for mortality in zebrafish early life stage was 6.4μM (2.8 mg/L) (Noyes et al., 2015).

The substance is not PBT/vPvB according to ECHA. The toxicity of this compound appears to be low, however, this should be interpreted with caution as no data on endocrine effects were assessed.

3.11 TBPP/TTBPP

A recent report on Environmental and health screening profiles of phosphorous flame retardants (Lassen et al., 2016) evaluated TBPP to have high hazard for the human health effects; systemic toxicity, moderate hazard for carcinogenicity, reproductive toxicity, neurotoxicity, skin sensitization and skin irritation, and low hazard for mutagenicity, developmental toxicity, acute mammalian toxicity and eye irritation. Very high hazard for acute and chronic aquatic toxicity was proposed (based on data from US EPA 2014a, 2014b, 2015 and summarized in Lassen et al., 2016).

No results on the ECHA registered substances page was found when searching for this compounds cas number. No effect on mortality, endocrine systems, development or nerotoxicity was found by searching the new literature. Due to the evaluation performed by Lassen et al., (2016) of very high hazard for acute and chronic aquatic toxicity, further studies of this substance is warranted.

3.12 BPDPP/tBPdPP

No results on the ECHA registered substances page was found when searching for this compounds cas number. The 120 hpf lowest effect level for mortality in zebrafish early life stage was reported to be 0.064 μM (0.02 mg/L) (Noyes et al., 2015).

Limited data on endocrine disruption and reproduction effects were obtained for tBPdPP. However, one study using the nematode C. elegans found that the compound affects reproduction with a lowest effect concentration of 16 μM (6.1 mg/L) (Behl et al., 2016).

The developmental effects of tBPdPP was investigated in the zebrafish embryo and delayed progression, yolc sac edema, effect on development of axis, eyes, snout, and jaw, as well as pericardial edema, developmental effects on pectoral fin and caudal fin was observed. The lowest effect level for all endpoints was 64 μM (24.5 mg/L) (Noyes et al., 2015). The development of zebrafish embryo showed a POD of 9.8 μM (3.75 mg/L), whereas the development of C. elegans larvae showed a POD of 3.3 μM (1.3 mg/L) (Behl et al., 2015) and a lowest effective concentration of 2.50 μM (0.96 mg/L) in a later study (Behl et al., 2016).

Developmental neurotoxicity was investigated in *in vitro* assays and the neuroprogenitor proliferation in human neuroprogenitor (hNP1) cells showed a POD of 7.2 μM (2.75 mg/L), whereas the rat neurite outgrowth in the rat primary cortical cultures showed a POD of 14.9 μM (5.70 mg/L), and the human neurite outgrowth in the human neurons (hN2) cells showed a POD of 4.1 μM (1.57 mg/L) (Behl et al., 2015).

The reported effect data indicate potential effects on reproduction and development.

3.13 bBPPP

No results on the ECHA registered substances page was found when searching for this compounds cas number. No effect on mortality was found by searching the new literature.

3.14 TEP

Toxicity tests with TEP showed a NOEC of 127 mg/L and an EC50 of 901 mg/L for algae, a long term NOEC of 31.6 mg/L and a short term EC50 of 900 mg/L for aquatic invertebrates and a short term EC50 of 2100 mg/L for fish (ECHA). The acute toxicity in the fish embryo test with zebrafish was given as a 96h LC50 of 1250 mg/L (Du et al., 2015).

The neurotoxic potential of TEP was assessed to be low (Hendriks and Westerink, 2015), and the EC50 for pericardial edema in zebrafish embryo was observed at 1240 mg/L (Du et al., 2015). TEP is not considered to be PBT/vPvB according to ECHA. The freshwater PNEC is set to 0.632 mg/L (af=50) and marine water PNEC is set to 0.063 mg/L (af=500) (ECHA). Based on the current data, the substance does not seem to fulfil the T criteria. However, no information regarding endocrine effects have been assessed.

3.15 BDPP/DPhBP

No results on the ECHA registered substances page was found when searching for this compounds cas number. No effect on mortality was found by searching the new literature.

3.16 DBPP/DBPHP

No results on the ECHA registered substances page was found when searching for this compounds cas number. No effect on mortality was found by searching the new literature.

3.17 TXP/TDMPP

The substance has a harmonised classification according to the CLP regulation as reprotoxic (Repr. 1B).
Toxicity tests with TXP have resulted in a NOEC and EC50 for algae of 0.112 mg/L and >1.011 mg/L, respectively. The long term NOEC and short term EC50 were 0.184 mg/L and 0.060 mg/L for aquatic invertebrates, and the fish short term EC50 was >1.119 mg/L (ECHA). Although the substance can be

considered to fulfill the criteria for persistency and toxicity under REACH, it does not fulfill the criteria for bioaccumulation (ECHA) as specified in REACH Annex XIII. Due to the fulfilment of T criteria and classification as Repr. 1B, this substance might be of environmental concern.

3.18 IPP

A recent report on Environmental and health screening profiles of phosphorous flame retardants (Lassen et al., 2016) evaluated IPP to have high hazard for the human health effects; reproductive toxicity, systemic toxicity, and neurotoxicity, moderate hazard for carcinogenicity and developmental toxicity, and low hazard for mutagenicity, acute mammalian toxicity, skin sensitization, skin irritation and eye irritation. Very high hazard for acute and chronic aquatic toxicity was proposed (based on data from US EPA 2014a, 2014b, 2015 and summarized in Lassen et al., 2016).

The compound IPP had a NOEC of 0.31 mg/L and an EC50 of >2.5 mg/L for algae, a long term NOEC and short term EC50 of 0.006 mg/L (test substance was Kronitex 200) and >1000 mg/L respectively. The toxicity towards fish was reported as a NOEC of 0.024 mg/L (test substance was Kronitex 200) and 4.46 mg/L (ECHA). The 120 hpf lowest effect level for mortality on the early life stage of zebrafish was 0.0064 μM (0.003 mg/L) (IPP-2), 0.064 μM (0.029) (IPP-3) and 64 μM (29 mg/L) (IPP-1) (Noyes et al., 2015).

Limited data on endocrine disruption and reproduction effects were obtained for IPP. However, one study using the nematode C. elegans found that the compound affects reproduction with a lowest effect concentration of 10 μM (4.5 mg/L) (Behl et al., 2016).

The developmental effects of IPP was investigated in zebrafish embryos and effects including delayed progression (24 hpf), yolc sac edema, effects on developmental axis, pericardial edema and effects on pectorial fin, caudal fin and touch responses was observed after 120 hpf. All endpoints had a lowest effect level of 64 μM (29 mg/L) (Noyes et al., 2015). The POD for zebrafish embryonic development was 4.9 μM (2.2 mg/L) (Behl et al., 2015). Effects on development was also observed in C. elegans larvae with a POD of 3.2 μM (1.45 mg/L) (Behl et al., 2015) and a lowest effective concentration of 1.60 μM (0.72 mg/L) (Behl et al., 2016).

In vitro assays also showed the potential for developmental and developmental neurotoxicity of IPP with POD for activity in mouse stem cell differentiation of 66.1 μM, a POD for neuroprogenitor proliferation I human neuroprogenitor (hNP1) cells of 8.7μM, a POD for rat neurite outgrowth in rat primary cortical cultures of 12.7 μM and a POD for human neurite outgrowth in human neurons (hN2) cells of 13.9 μM (Behl et al., 2015).

Although the substance is considered to fulfill the criteria for toxicity, it is not classified as PBT/vPvB due to lack of fulfillment of the persistency and bioaccumulation criteria (ECHA).

3.19 Other reported effects

Only a few of the recent publications have investigated other types of effects including DNA damage and repair, oxidative stress and dioxin like effects. It has been shown that DNA damage repair and cell cycle pathways, including DNA replication, cell cycle, non-homologous end-joining (NHEJ) and base excision repair (BER) pathways, were strongly affected (hampered) in adult zebrafish after exposure to TPHP (Du et al., 2016).

Dioxin like effects mediated by the arylhydrocarbon receptor (AhR) are believed to be caused mainly by planar aryl hydrocarbons and compounds with structural similarity to these. Long-term exposure (6 months) to TDCPP significantly induced the phase I metabolic enzymes 7-ethoxyresorufin O-deethylase (EROD) and 7-methoxyresorufin O-demethylase (MROD) in zebrafish. The mRNA expression of genes related to Phase I and II metabolic enzymes, were also significantly upregulated in exposed fish (Xu et al., 2015).

Oxidative stress will often occur after exposure to pollutants as free radicals may be produced during their metabolisation. An *in vivo* study investigating growth effects and effects on the oxidative stress in male mice after exposure to TPP and TCEP found that both TPP- and TECP-treatments decreased the body weights and testes weights of the mice. Exposure of TCEP also resulted in reduced liver weights. Both compounds induced oxidative stress as indicated by reduced GSH content in the liver, increased activity of antioxidant enzymes SOD, CAT and GPX in the liver and decreased activity of GST. Generally, the transcriptional patterns of Sod1, Sod2, Gpx1, Gpx2and Cat in response to TPP and TCEP treatments were similar to the change in the activities of their respective enzymes (Chen et al., 2015a). Similar results were obtained *in vitro* with TM3 Lydig cells where significant increases in superoxide dismutase (SOD), catalase(CAT), glutathione peroxidase (GPX) and glutathione S-transferase (GST) activities and their respective gene expression occurred in a dose-dependent and/or time-dependent manner in TPP or TCEP exposed cells (Chen et al., 2015b).

Exposure of zebrafish for 7 days to 0.050 and 0.300 mg/L followed by metabolimic analysis resulted in 19 Significantly changed metabolites which were indicative of induced metabolic disruption in the zebrafish liver. The metabolites were involved in carbohydrate metabolism (glucose, UDP-glucose, glycolate, fumarate, succinate, and lactate), lipid and fatty acid metabolism (choline, acetylcarnitine, esterified cholesterol, arachidonic acid [ARA], timnodonic acid [EPA], linoleic acid and fatty acids identified by α H2), amino acid metabolism (glutamate, glutamine and leucine), and osmolyte metabolism (TMAO, dimethylamine [DMA]). It was also observed that TPhP had comprehensive toxic effects in zebrafish liver after a one-week exposure period even at the low dose (0.050mg/L) (Du et al., 2016).

4 Bioaccumulation & biomagnification

OFPR are found in several biological samples often in the lower end of the found chain such as mussels, krill, prawns (Miljødirektoratet 2014, 2015, 2016). Although higher levels of OFPRs are found in for example eel, carp, perch or herring this is often in relation to local sources (Wei et al. 2015). In table 2 BCF are compiled from the literature and databases including chemspider and pubchem. Using the PBT criteria for bio accumulation potential (BCF > 2000) listed in Table all OFPS are below this value except for EHDPP where BCF range from 855 to 64900 depending on the reference and for TEHP and TBPP where only one value derivate from chemspider was found (1000000), no further reference or supporting data for this compound was found. Based on the structure of this aliphatic OPFRs and in relation to other aliphatic OPFRs this value seems extremely large and is moist probably based on prediction models. Likewise, for the aromatic OPFR TBPP where this large BCF is not in relation to the other aromatic OPFRs.

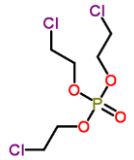
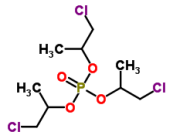
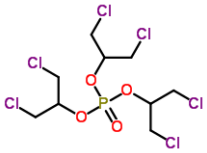
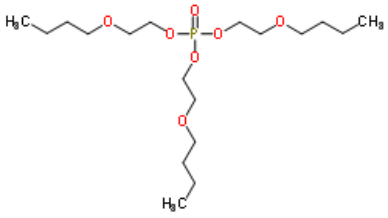
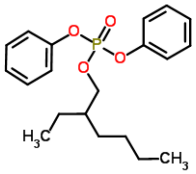
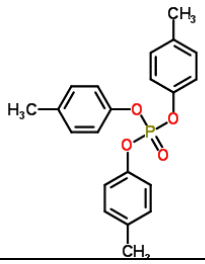
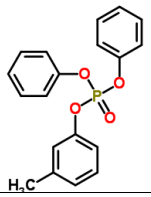
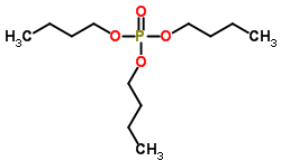
Measured data of the physical properties of the new OPFRs for the persistence and bio accumulation is still not available from the international peer reviewed literature and most assessments depend on estimates, models calculations and predictions. This is evident from two recent publications were half lives in for example water can vary two orders of magnitude for the different OPFRs (Zhang et al. 2015). Depending on estimated half-life in water, air and soil and emission scenarios to air and soil. These fugacity based models which depend on Kow and Kaw predict that OPFRs end up in the soil or water phase (Liagkourdis et al. 2015). Most OPFRS are relative persistent in the soils and sediment but not in water.

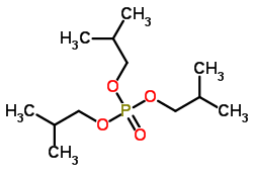
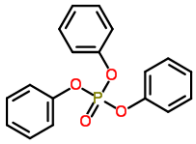
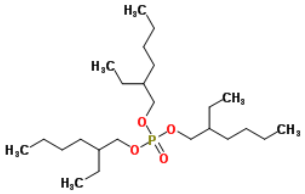
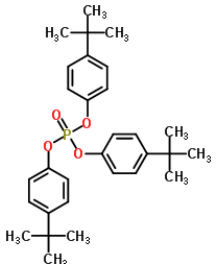
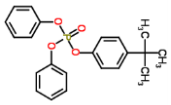
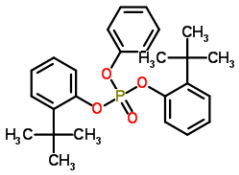
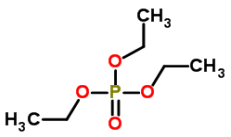
Biomagnification for the chlorinated OPFRs; TCEP, TCIPP, TDCIP, the aliphatic OPFRs; TiPB TEHP and the aromatic OPFRs; TPHP, EHDPP and the carboxylate OPFR; TBOEP was recently investigated by Brandsma et al. in relation to brominated FRs. The conclusion of this study on biota in the Western Schelde was that the investigated OPFRs showed thropic dilution with negative Tropic Magnification Factors (TMFs) for the total food web, but that a tendency for biomagnification was seen for TCEP, TCIP and TBOEP. Interesting TBOEP was one of the few OPFRs found in species higher up the food chain in recent Norwegian samples (Miljödirektoratet 2014, 2015, 2016). TBEOP was found in herring gull blood, herring muscle and cod liver. The BCF value in the recent literature is however under the criteria for bioaccumulation and ranged from 25-1080. In addition, TBOEP was stated to be biodegradable and photodegradable in water (Gramatica et al. 2016).

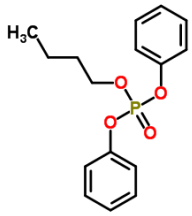
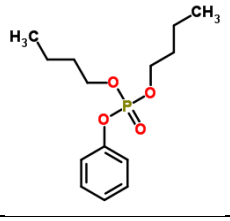
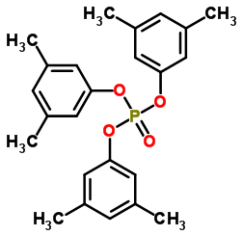
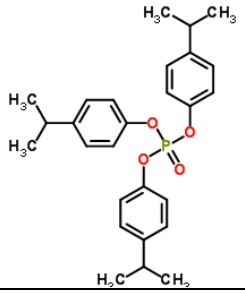
All OPFRs compounds are susceptible to biodegradation via hydrolysis of the phosphate ester group by enzymes referred to as organophosphate hydrolase or phosphotriesterase (Waaijers and Parsons 2016) and seem to be metabolized relatively quickly in biota including humans. Recent studies showing metabolism of several OPFRs is discussed in detail in section 2.3 and clearly show metabolism in humans exposed through the indoor environment.

Based on limited measured data and mainly predicted BCF values bioaccumulation of the aromatic OPFRs; EHDPP, TCP structurally have the potential to bio accumulate. This is in agreement with a recent report from the Ministry of the Environment and Food in Denmark (Lassen et al. 2016). Also TEHP and TBPP might bio accumulate but this is based on only one predicted value, this value seems extremely high and has not been experimentally validated. TBEOP BCF value fails to meet the bio accumulation criteria with literature values between 26 and 1080, however TBOEP has been detected in recent Norwegian samples higher up in the food chain and showed some degree of biomagnification in a food chain.

***Table 2** -All investigated compounds, abbreviation, structure and bio concentration factor (BCF)*

Chemical	Abbreviation	Structure[e]	BCF [a&b]
Tris(2-chloroethyl) phosphate	TCEP		1,37[a] / 0,42[b]
Tris(2-chloro-1-methylethyl) phosphate	TCPP / TCIPP		42,4[a] / 3,26[b]
Tri(1,3-dichloro-2-propyl) phosphate	TDCPP / TDCIPP		13,5[a] / 21,4[b]
Tris(2-butoxyethyl) phosphate	TBEP / TBOEP		1080[a] / 25,56[b]
2-ethylhexyl diphenyl phosphate	EHDPP / EHDPHP		64900[a] / 855[b] / 934[d]
Tris(methylphenyl) phosphate / Tricresyl phosphate	TCP / TMPP / TCrP		8560[b]
Cresyl diphenyl phosphate	CDPhP / CDPP /MPDPP		110 to 1420[c]
Tri-n-butylphosphate	TBP / TnBP		1030[a] / 39,81[b]

Chemical	Abbreviation	Structure[e]	BCF [a&b]
Tri-iso-butylphosphate	TBP / TiBP		391[a] / 19,51[b]
Triphenyl phosphate	TPP / TPHP		113[a&b]
Tris(2-ethylhexyl) phosphate	TEHP		1,0*10^{6} [a&b]
Tris(p-tert-butylphenyl) phosphate	TBPP / TTBPP		1,0*10^{6} [e]
4-tert-Butylphenyl diphenyl phosphate	BPDPP / tBPdPP		778
bis(t-butylphenyl) phenyl phosphate)	bBPPP		< 2000
Triethyl phosphate	TEP		3,88[a] / 3,16[b]

Chemical	Abbreviation	Structure[e]	BCF [a&b]
Butyl diphenyl phosphate	BDPP /DPhBP		608 [e]
Dibutyl phenyl phosphate	DBPP /DBPHP		< 2000
Trixylyl phosphate	TXP / TDMPP		480[b] /1900[d]
Phenol, isopropylated, phosphate (3:1) - tri(isopropyl phenyl) phosphate	IPP		1986[d]

[a]Gao-Ling Wei et al. 2015. Review: Organophosphorus flame retardants and plasticizers: Sources,occurrence, toxicity and human exposure. Environ. Pollut. 196, 29-46.
[b]Rui Hou et al. 2016. REVIEW of OPFRs in animals and humans: Absorption, bioaccumulation, metabolism, and internal exposure research. Chemosphere 153, 78-90.

[c] Pubchem (www.pubchem.ncbi.nlm.nih.gov)

[d] UK Environment Agency 2009

[e] Chem Spider (chemspider.com), Chemical Book (chemicalbook.com), International Programme on Chemical Safety (inchem.org), Wikipedia

5 Summary of PBT behavior

The three chlorinated OPFRs (TCEP, TCPP and TDCPP) all show EDC toxicity, they are relatively persistent but do not bio accumulate. Despite this they are often found in biota in the Norwegian environment mainly TCEP in lower organisms and even in polar regions in Capelin (TCEP; TCIPP) and Kittiwake (TCEP) Kongsfjorden. Only TCEP is acute toxic on zebrafish embryos.

Of the aliphatic OFPRs, TnBP is classified as a carcinogenic, but the bio accumulation potential is below the PBT criteria. TiBP also show a low bio accumulation potential but no recent toxicity data is available, also little recent data is available on persistence in the environment. TEHP shows a high bio accumulation potential but here we only found one recent predicted value, which was extremely high (1000000) and might not reflect its behavior in the environment. Persistence was recorded as low and no recent data on toxicity was found for THEP. TEP might have some bio accumulation potential is not considered to be persistent and acute of chronic toxic and no recent data on EDC toxicity was found.

Of the aromatic OPFRs, EHDPP and TCP were reported to have a high bio accumulation potential and TCP was found to be acute toxic to zebrafish larvae, but no data on EDC toxicity was found. Both compounds were not found to be persistent and only occasional found in biological samples.

TPP, and IPP were both found to be both acute/chronic and EDC toxic, BPDPP was found to be EDC toxic, but no recent data was found for CDPP, TBPP, BPPP, BDPP, DBPP. TXP was only found to be acute/chronic toxic while no data on EDC toxicity was found. This is somewhat worrisome for both TXP and IPP because of their potential bio accumulation potential and very little monitoring data exists for both compounds. Also TEP and especially TBPP are predicted to have medium to high bioaccumulation potential and toxicity data is still lacking. TEP has been detected in biological samples mainly fish and recently in mussels and herring in Norway. No recent environmental data on TBPP in biological samples was found in addition to the lack of toxicity data.

Strictly applying the PBT assessment criteria; P: half-life above 60 days in marine water, 40 days in fresh water, 180 days in marine sediment or 120 in fresh water sediment, B: BCF above 2000 and T: chronic NOEC below 0.01 mg/L or human health end points or EDC effects, no OPFR would qualify. TXP and IPP are both possibly toxic, data on persistence is missing but the predicted BCF is very close to 2000. The bioaccumulation criteria should be normalized to 5% lipids which seems somewhat irrelevant for most OPFRs because they do not seem to accumulate in lipid tissues and other accumulation mechanisms similar to persistent fluor compounds might occur. However, no further information on the bioaccumulation mechanisms of OPFRs was found in the literature.

Because BCF are often predicted environmental monitoring data especially in biological samples from remote or Arctic regions are of importance. TBOEP was also found to be show EDC toxicity. This might be a concern for the group of carboxylated OPFRs, although it is not known if this true for all carboxylated OPFRs.

The use of monitoring data is not without any complications as the analysis of OPFRS is complicated, especially in sample from remote areas with relatively low concentration compared to indoor air concentrations in buildings where OPFRs or products with OPFRs are used. International QA/QQC studies have shown that there might be a considerable variation in data quality because of blank problems caused by OPFRs in the laboratory environment or the use of consumables contaminated with OPFRs (Brandsma et al. 2013).

Table 3 *-All investigated compounds with indications persistence, bioaccumulation and observed effects*

Chemical	Abbreviation	Persistence	Bio accumulation	Acute and Chronic Toxicity	EDC Toxicity
Tris(2-chloroethyl) phosphate	TCEP	Medium	Low	Yes - EC50 in zebrafish embroy test = 0.0018 mg/L	Yes
Tris(2-chloro-1-methylethyl) phosphate	TCPP / TClPP	Medium	Low	No	Yes
Tri(1,3-dichloro-2-propyl) phosphate	TDCPP / TDCIPP	Medium	Low	No	Yes
Tris(2-butoxyethyl) phosphate	TBEP / TBOEP	Low	Low	No	Yes
2-ethylhexyl diphenyl phosphate	EHDPP / EHDPHP	Low	Medium	No data	No data
Tris(methylphenyl) phosphate / Tricresyl phosphate	TCP / TMPP / TCrP	Low	Medium	Yes - Lowest effect level for mortality on zebrafish larvae = 0.002 mg/L	No data
Cresyl diphenyl phosphate	CDPhP / CDPP /MPDPP	Low	Low	No	No data
Tri-n-butylphosphate	TBP / TnBP	No recent data	Low	Yes - classified as carcinogenic (carc 2.)	No. Only one in vitro study (gene reporter study) and high concentrations
Tri-iso-butylphosphate	TBP / TiBP	No recent data	Low	No	No data
Triphenyl phosphate	TPP / TPHP	Low	Low	Yes - 120hpf lowest effect level for mortality in zebrafish early life stage was 0.0064 µM (0.002 mg/L	Yes
Tris(2-ethylhexyl) phosphate	TEHP	Low	High	No	No data

Chemical	Abbreviation	Persistence	Bio accumulation	Acute and Chronic Toxicity	EDC Toxicity
Tris(p-tert-butylphenyl) phosphate	TBPP / TTBPP	Medium	High	No data	No data
4-tert-Butylphenyl diphenyl phosphate	BPDPP / tBPdPP	Low	Low	No	Yes
bis(t-butylphenyl) phenyl phosphate)	bBPPP	Yes	Low	No data	No data
Triethyl phosphate	TEP	No recent data	Low	No	No data
Butyl diphenyl phosphate	BDPP /DPhBP	Low	Low	No data	No data
Dibutyl phenyl phosphate	DBPP /DBPHP	Yes	Low	No data	No data
Trixylyl phosphate	TXP / TDMPP	Medium	Medium	Yes - the substance has a harmonised classification according to the CLP Regulation as reprotoxic (Repr. 1B)	No data
Phenol, isopropylated, phosphate (3:1) - tri(isopropyl phenyl) phosphate	IPP	No recent data	Medium	Yes - lowest effect level for mortality on zebrafish larvae = 0.003 mg/L	Yes

[a] Gao-Ling Wei et al. 2015. Review: Organophosphorus flame retardants and plasticizers: Sources, occurrence, toxicity and human exposure. Environ. Pollut. 196, 29-46.
[b] Rui Hou et al. 2016. REVIEW of OPFRs in animals and humans: Absorption, bioaccumulation, metabolism, and internal exposure research . Chemosphere 153, 78-90.

[c] Pubchem (www.pubchem.ncbi.nlm.nih.gov)

[d] UK Environment Agency 2009
[e] Chem Spider (chemspider.com), Chemical Book (chemicalbook.com), International Programme on Chemical Safety (inchem.org), Wikipedia

6 Prioritization

Category 1 (potential risk limited data) **TXP** and **IPP**
Data shows acute/chronic toxicity but persistence and bio accumulation potential is unclear. Very little reliable monitoring data exists both compounds are relatively large molecules with both phenyl groups and alkyl substitution.

Category 2 (potential risk, BCF/persistence unclear): **TBOEP**
New data shows that TBOEP shows EDC disrupting toxicity, the accumulation potential is unclear and despite the low persistence TBOEP has recently been found in biological samples higher up the food chain.

Category 3 (limited toxicity data, potential persistent, predicted BCF): **THEP**, **TBPP**, **BPPP**, **DBPP**.
No recent toxicity data was found for TBPP, BPPP and DBPP all three compound are show to be persistent. The predicted bio accumulation potential for THEP and TBPP is high and for BPPP and DBPP is low. Only limited data of levels in biological samples available.

Category 4 (Well studied, found in biota low bioaccumulation): **TCEP**, **TCPP**, **TDCPP**
The three chlorinated tri phosphate compounds are relatively well studied. Recent data shows EDC toxicity for all three compounds and all three compounds are abundant in biological and environmental samples. However, they do not bio accumulate and seem to biodegrade as soon in recent publications. Levels higher up the food chain are often low.

7 Conclusion

Research in the field of risk assessment of replacement chemicals for brominated flame retardants is rapidly expanding with more than 70 peer reviewed publication in the international literature. These publications show a variety of data including toxicity, environmental levels and persistence or bioaccumulation assessments. Despite this there still is a lack of information for several of the 19 OPFRs included in this literature review. For 11 of the compounds no EDC toxicity data was available and for 5 no recent acute/chronic toxicity data was found.

Concerning persistence there is more data available for 15 of the 19 compounds is available, showing that 9 compound might be persistent. This includes the three chlorinated OPFRs (TCEP, TCPP and TDCPP) but also aromatic OPFRs (TBPP, BPPP, DBPP, TXP and IPP).

Only very few measured BCFs are available and most data in the literature is based on QSAR predictions or other model calculations. BCFs were available for all 19 compounds but varied considerably between the different approaches and could easily differ an order of magnitude. Based on the available data two compounds (TEHP and TBPP) were predicted to have an extreme high bioaccumulation potential whereas for four compounds medium (TXP and IPP) or medium to high (EHDPP and TCP) BCF were predicted or calculated.

The 19 OPFRS included in this study were mostly found in the abiotic environment in the indoor environment including air and dust and in water samples mostly in the effluents or near WWTP or in sediments. There is a lot of data on the three chlorinated OPFRs (TCEP, TCPP and TDCPP) in biota and also a reasonable number of studies for TCP, TBP, TPP and TEHP. But much less data on TBPP, BPDPP, BPPP, DBPP, TXP and IPP in biological samples. TEP was only found in a one study, BDPP in only a few of a large number of Arctic samples. There is definitely a lack of high quality analytical data for several of the compounds as shown in recent QA/QC studies. One major challenge here is laboratory blank levels of several of the OPFRs in laboratory air. With regard to OPFRs levels it was found not be relevant to normalize to lipids, OPFRS do not seem to accumulate in lipids and as traditional persistent organic pollutants (POPs). They seem to behave more like persistent fluor compounds (PFAS) although no information on the accumulation of OPFRs in biota was found.

Of the 19 compounds studied, the aromatic tri substituted OPFRs TXP and IPP are of concern because there is proof of toxicity and predicted bio accumulation. Only very little monitoring data in biota of TXP and IPP exist. In addition, TBOEP is a compound of interest, this compounds have shown EDC toxicity and has recently been found in several biological samples even higher up the food chain.

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9 Appendix I. Summary of toxicity data.

Compound	Abbreviation	Effect type	Measured endpoint	Assay/species	Reliability[a]	Reference
Tris(2-chloroethyl) phosphate	TCEP	Mortality	120 hpf lowest effect level = 0.0064 μM (1.83 μg/L)	*Danio rerio* early life stage		(Noyes et al., 2015)
Tris(2-chloroethyl) phosphate	TCEP	Acute toxicity	96h LC50 = 202 mg/L	*Danio rerio* embryo		(Du et al., 2015)
Tris(2-chloroethyl) phosphate	TCEP	Growth inhibition	Growth inhibition, NOEC ~72 mg/L	*Pseudokirchneriella subcapitata*	2	ECHA[b]
Tris(2-chloroethyl) phosphate	TCEP	Growth inhibition	EC_{50} for growth inhibition ~450 mg/L	*Pseudokirchneriella subcapitata*	2	ECHA[b]
Tris(2-chloroethyl) phosphate	TCEP	Short term toxicity	Immobility EC_{50} ~170 mg/L	*Daphnia magna*	2	ECHA[b]
Tris(2-chloroethyl) phosphate	TCEP	Neurotoxicity	Genes related to the nervous system	Embryo test with *Danio rerio*		(Sun et al., 2016b)
Tris(2-chloroethyl) phosphate	TCEP	Developmental toxicity	Body length	Embryo test with *Oryzias latipes*		(Sun et al., 2016a)
Tris(2-chloroethyl) phosphate	TCEP	Developmental toxicity	Reduced average speed at 6250 μg/L	Embryo test with *Danio rerio*		(Sun et al., 2016b)
Tris(2-chloroethyl) phosphate	TCEP	Developmental toxicity	96h EC50 of pericardial edema = 179 mg/L	*Danio rerio* embryo		(Du et al., 2015)
Tris(2-chloroethyl) phosphate	TCEP	Steroidogenesis	Altered gene expression	Juvenile *Salmo salar*		(Arukwe et al., 2016)
Tris(2-chloroethyl) phosphate	TCEP	Oxidative stress	Enzyme activity and gene expression	male ICR *Mus musculus*		(Chen et al., 2015a)
Tris(2-chloroethyl) phosphate	TCEP	Oxidative stress	Enzyme activity and gene expression	murine Leydig cell line TM3		(Chen et al., 2015b)
Tris(2-chloroethyl) phosphate	TCEP	Endocrine disruption	decreases in the number of leydig cells, Sertoli cells and spermatogenic cells, absolute disintegration of seminiferous tubule structure	male ICR *Mus musculus*		(Chen et al., 2015a)
Tris(2-chloroethyl) phosphate	TCEP	Endocrine disruption	Reduced testosterone levels and altered expression of genes related to T synthesis	murine Leydig cell line TM3		(Chen et al., 2015b)
Tris(2-chloroethyl) phosphate	TCEP	Endocrine disruption (thyroid)	plasma free triiodothyronine (FT3) concentrations and free thyroxine (FT4) (22 ng OPFR/g kestrel/d) daily (21 d)	*Falco sparverius*		(Fernie et al., 2015)
Tris(2-chloro-1-methylethyl) phosphate	TCPP / TCIPP	Acute toxicity	96h LC50 = 13,5 mg/L	*Danio rerio* embryo		(Du et al., 2015)
Tris(2-chloro-1-methylethyl) phosphate	TCPP / TCIPP	Endocrine disruption	PXR agonistic activity	Gene reporter assay		(Kojima et al., 2016)

Compound	Abbreviation	Effect type	Measured endpoint	Assay/species	Reliability[a]	Reference
Tris(2-chloro-1-methylethyl) phosphate	TCPP / TCIPP	Endocrine disruption (thyroid)	plasma free triiodothyronine (FT3) concentrations (22 ng OPFR/g kestrel/d) daily (21 d)	*Falco sparverius*		(Fernie et al., 2015)
Tris(2-chloro-1-methylethyl) phosphate	TCPP / TCIPP	Developmental toxicity	96h EC50 of pericardium edema =22,8 mg/L	*Danio rerio* embryo		(Du et al., 2015)
tri(1,3-dichloro-2-propyl)phosphate	TDCPP / TDCIPP	Mortality	120hpf lowest effect level =64 μM	*Danio rerio* early life stage		(Noyes et al., 2015)
tri(1,3-dichloro-2-propyl)phosphate	TDCPP / TDCIPP	Acute toxicity	96h LC50 = 0,418 mg/L	*Danio rerio* embryo		(Du et al., 2015)
tri(1,3-dichloro-2-propyl)phosphate	TDCPP / TDCIPP	Growth inhibition	Growth inhibition, NOEC =6 mg/L	*Pseudokirchnerella subcapitata*	3	ECHA[b]
tri(1,3-dichloro-2-propyl)phosphate	TDCPP / TDCIPP	Growth inhibition	Growth inhibition, EC_{50}(biomass) = 12 mg/L	*Pseudokirchnerella subcapitata*	3	ECHA[b]
tri(1,3-dichloro-2-propyl)phosphate	TDCPP / TDCIPP	Short term toxicity	EC_{50} = 1.4 mg/L	*Oncorhynchus mykiss*	3	ECHA[b]
tri(1,3-dichloro-2-propyl)phosphate	TDCPP / TDCIPP	Neurotoxicity	Various	Various		(Hendriks and Westerink, 2015)
tri(1,3-dichloro-2-propyl)phosphate	TDCPP / TDCIPP	Neurotoxicity	Reduction in expression of neurotrophic factor genes	*Gobicypris rarus*		(Yuan et al., 2016)
tri(1,3-dichloro-2-propyl)phosphate	TDCPP / TDCIPP	Neurodevelopment	Delayed progression and caudal fin	*Danio rerio* early life stage		(Noyes et al., 2015)
tri(1,3-dichloro-2-propyl)phosphate	TDCPP / TDCIPP	Possible neurodevelopmental effects	Early-incubation mortality, behaviour, brain histopathology (reduced number of degenerate Purkinje cells)	White leghorn chicken		(Bradley et al., 2015)
tri(1,3-dichloro-2-propyl)phosphate	TDCPP / TDCIPP	Neurodevelopmental toxicity	Reductions of dopamine, serotonin and downregulation of nervous system development genes	*Danio rerio*		(Wang et al., 2015a) (Wang et al., 2015b)
tri(1,3-dichloro-2-propyl)phosphate	TDCPP / TDCIPP	Developmental toxicity	C elegans larval development, point of departure = 9,8μM	*C. elegans*		(Behl et al., 2015)
tri(1,3-dichloro-2-propyl)phosphate	TDCPP / TDCIPP	Developmental toxicity	C elegans larval development, lowest effective concentration = 13 μM	*C. elegans*		Behl at al., 2016
tri(1,3-dichloro-2-propyl)phosphate	TDCPP / TDCIPP	Developmental toxicity	Mouse stem cell differentiation, point of departure (POD[c])= 44,1μM), cytotoxicity also observed	Mouse embryonic stem cells		(Behl et al., 2015)
tri(1,3-dichloro-2-propyl)phosphate	TDCPP / TDCIPP	Developmental toxicity	Zebrafish embryonic development, point of departure = 8,9μM), mortality also occurring	*Danio rerio* embryo		(Behl et al., 2015)
tri(1,3-dichloro-2-propyl)phosphate	TDCPP / TDCIPP	Developmental toxicity	96h EC50 of pericardium edema = 1,65 mg/L	*Danio rerio* embryo		(Du et al., 2015)
tri(1,3-dichloro-2-propyl)phosphate	TDCPP / TDCIPP	Behavior	Hyperactivity, predator escape, behavior in novel environment, startle habituation and social affiliation	*Danio rerio*		(Oliveri et al., 2015)

Compound	Abbreviation	Effect type	Measured endpoint	Assay/species	Reliability[a]	Reference
tri(1,3-dichloro-2-propyl)phosphate	TDCPP / TDCIPP	Endocrine disruption	PXR agonistic activity, AR and GR antagonistic activity	Gene reporter assay		(Kojima et al., 2016)
tri(1,3-dichloro-2-propyl)phosphate	TDCPP / TDCIPP	Endocrine disruption (anti-androgen)	Altered levels of mRNA and protein accumulation of AR target genes	Human prostate cancer cell line		(Reers et al., 2016)
tri(1,3-dichloro-2-propyl)phosphate	TDCPP / TDCIPP	Endocrine disruption (thyroid)	Decrease in plasma thyroxine, 3,5,3'-triiodothyronine	*Danio rerio*		(Wang et al., 2015a)
tri(1,3-dichloro-2-propyl)phosphate	TDCPP / TDCIPP	Endocrine disruption/reproduction	Reduced fecundity (egg production)	*Danio rerio*		(Wang et al., 2015c)
tri(1,3-dichloro-2-propyl)phosphate	TDCPP / TDCIPP	Endocrine disruption (thyroid)	Reduction in plasma T4 and T3 in females	*Danio rerio*		(Xu et al., 2015)
tri(1,3-dichloro-2-propyl)phosphate	TDCPP / TDCIPP	Endocrine disruption (thyroid	plasma free triiodothyronine (FT3) concentrations and total thyroxine (TT4) (22 ng OPFR/g kestrel/d) daily (21 d)	*Falco sparverius*		(Fernie et al., 2015)
tri(1,3-dichloro-2-propyl)phosphate	TDCPP / TDCIPP	Reproduction	Reduced number of eggs	*Danio rerio*		(Zhu et al., 2015)
tri(1,3-dichloro-2-propyl)phosphate	TDCPP / TDCIPP	Reproduction	lowest effective concentration = 130 μM	*C. elegans*		(Behl et al., 2016)
tri(1,3-dichloro-2-propyl)phosphate	TDCPP / TDCIPP	Dioxin like effects	Induction of EROD and MROD (Phase 1 biotransformation)	*Danio rerio*		(Xu et al., 2015)
Tris(2-butoxyethyl) phosphate	TBEP / TBOEP	Mortality	96hpf and 129 hpf LC50 =288.54 μg/L	*Danio rerio* early life stage		(Ma et al., 2016)
Tris(2-butoxyethyl) phosphate	TBEP / TBOEP	Mortality	120hpf lowest effect level = 6.4 μM (2.55 mg/L)	*Danio rerio* early life stage		(Noyes et al., 2015)
Tris(2-butoxyethyl) phosphate	TBEP / TBOEP	Acute toxicity	96h LC50=3,34 mg/L	*Danio rerio* embryo		(Du et al., 2015)
Tris(2-butoxyethyl) phosphate	TBEP / TBOEP	Acute toxicity	48h LC50 = 147 mg/L	*Daphnia magna*		(Giraudo et al., 2015)
Tris(2-butoxyethyl) phosphate	TBEP / TBOEP	Growth inhibition	Growth inhibition, NOEC = 7.6 mg/L	*Pseudokirchnerella subcapitata*	1	ECHA[b]
Tris(2-butoxyethyl) phosphate	TBEP / TBOEP	Growth inhibition	Growth inhibition, EC50 (yield) = 33 mg/L	*Pseudokirchnerella subcapitata*	1	ECHA[b]
Tris(2-butoxyethyl) phosphate	TBEP / TBOEP	Short term toxicity	Short term EC50 = 75 mg/L	*Daphnia magna*	4	ECHA[b]
Tris(2-butoxyethyl) phosphate	TBEP / TBOEP	Short term toxicity	Short term EC50 = 32 mg/L	*Oncorhynchus mykiss*	2	ECHA[b]
Tris(2-butoxyethyl) phosphate	TBEP / TBOEP	Endocrine disruption	PXR agonistic activity	Reporter gene assay		(Kojima et al., 2016)
Tris(2-butoxyethyl) phosphate	TBEP / TBOEP	Endocrine disruption (thyroid)	plasma free triiodothyronine (FT3) concentrations and total thyroxine (TT4) (22 ng OPFR/g kestrel/d) daily (21 d)	*Falco sparverius*		(Fernie et al., 2015)
Tris(2-butoxyethyl) phosphate	TBEP / TBOEP	Endocrine disruption	Decreased egg production, lowered hatching rates	Adult *Danio rerio* and fertilized eggs		(Kwon et al., 2016)

Compound	Abbreviation	Effect type	Measured endpoint	Assay/species	Reliability[a]	Reference
Tris(2-butoxyethyl) phosphate	TBEP / TBOEP	Endocrine disruption	ER genes	*Danio rerio* embryo/early life stage		(Ma et al., 2015)
Tris(2-butoxyethyl) phosphate	TBEP / TBOEP	Endocrine disruption	Genes involved in hormone synthesis	*Danio rerio* early life stage		(Ma et al., 2016)
Tris(2-butoxyethyl) phosphate	TBEP / TBOEP	reproduction	Decreased number of offspring	*Daphnia magna*		(Giraudo et al., 2015)
Tris(2-butoxyethyl) phosphate	TBEP / TBOEP	Developmental toxicity	Malformations	*Danio rerio* early life stage		(Ma et al., 2016)
Tris(2-butoxyethyl) phosphate	TBEP / TBOEP	Developmental toxicity	Hatchability, time to hatch, gross abnormality rate, heart rate, body length	Embryo test with *Oryzias latipes*		(Sun et al., 2016a)
Tris(2-butoxyethyl) phosphate	TBEP / TBOEP	Developmental toxicity	Reduced average speed at 6250 µg/L	Embryo test with *Danio rerio*		(Sun et al., 2016b)
Tris(2-butoxyethyl) phosphate	TBEP / TBOEP	Developmental toxicity	96h EC50 of pericardial edema= 4,10 mg/L	*Danio rerio* embryo		(Du et al., 2015)
Tris(2-butoxyethyl) phosphate	TBEP / TBOEP	Neurodevelopment	Yolc sac edema, lowest effect level = 6.4E-4µM	*Danio rerio* early life stage		(Noyes et al., 2015)
Tris(2-butoxyethyl) phosphate	TBEP / TBOEP	Neurotoxicity	Altered expression of genes related to the nervous system	Embryo test with *Danio rerio*		(Sun et al., 2016b)
2-ethylhexyl diphenyl phosphate	EHDPP / EHDPHP	Mortality	120hpf lowest effect level = 64 µM (23.2 mg/L)	*Danio rerio* early life stage		(Noyes et al., 2015)
2-ethylhexyl diphenyl phosphate	EHDPP / EHDPHP	Growth inhibition	Growth inhibition, NOEC =0.03 mg/L	*Pseudokirchnerella subcapitata*	4	ECHA[b]
2-ethylhexyl diphenyl phosphate	EHDPP / EHDPHP	Growth inhibition	Growth inhibition, EC_{50} = 0.2 mg/L	*Pseudokirchnerella subcapitata*	4	ECHA[b]
2-ethylhexyl diphenyl phosphate	EHDPP / EHDPHP	Long term toxicity	Long term NOEC = 0.18	*Daphnia magna*	4	ECHA[b]
2-ethylhexyl diphenyl phosphate	EHDPP / EHDPHP	Long term toxicity	Long term NOEC = 0.021-0.058	*Oncorhynchus mykiss*	4	ECHA[b]
2-ethylhexyl diphenyl phosphate	EHDPP / EHDPHP	Short term toxicity	Short term EC50 >0.38	*Lepomis macrochirus*	3	ECHA[b]
2-ethylhexyl diphenyl phosphate	EHDPP / EHDPHP	Neurodevelopment	Axis, pericaridal edema, 120hpf lowest effect level = 64µM	*Danio rerio* early life stage		(Noyes et al., 2015)
2-ethylhexyl diphenyl phosphate	EHDPP / EHDPHP	Developmental toxicity	C. elegans larval development, point of departure= 2,3µM (0.83 mg/L)	*C. elegans*		(Behl et al., 2015)
2-ethylhexyl diphenyl phosphate	EHDPP / EHDPHP	Developmental toxicity	C. elegans larval development, lowest effect level = 1.60 (0.58 mg/L)	*C. elegans*		
2-ethylhexyl diphenyl phosphate	EHDPP / EHDPHP	Developmental toxicity	Zebrafish embryonic development, point of departure=15,3µM, mortality also occurring	*Danio rerio* embryo		(Behl et al., 2015)
2-ethylhexyl diphenyl phosphate	EHDPP / EHDPHP	Developmental toxicity	Neuroprogenitor proliferation, point of departure= 13,2µM, cytotoxicity also occurring	Human neuroprogenitor (hNP1) cells		(Behl et al., 2015)

Compound	Abbreviation	Effect type	Measured endpoint	Assay/species	Reliability[a]	Reference
2-ethylhexyl diphenyl phosphate	EHDPP / EHDPHP	Developmental neurotoxicity	Human neurite outgrowth, point of departure= 6,9µM	Human neurons (hN2) cells		(Behl et al., 2015)
Tris(methylphenyl) phosphate / Tricresyl phosphate	TCP / TMPP	Mortality	24 and 120hpf lowest effect level = 0.0064 µM	*Danio rerio* early life stage		(Noyes et al., 2015)
Tris(methylphenyl) phosphate / Tricresyl phosphate	TCP / TMPP	Neurodevelopment	Delayed progression, yolc sac edema, axis, pericardial edema, touch responses	*Danio rerio* early life stage		(Noyes et al., 2015)
Tris(methylphenyl) phosphate / Tricresyl phosphate	TCP / TMPP	Development	Larval development, lowest effective concentration = 100µM	*C. elegans*		Behl et al., 2016
Tris(*o*-methylphenyl) phosphate	TOCP/o-TCP	Mortality	120hpf lowest effect level = 64 µM	*Danio rerio* early life stage		(Noyes et al., 2015)
Tris(*o*-methylphenyl) phosphate	TOCP/o-TCP	Toxicity (TOCP)	Inhibition of cell viability and induction of autophagy	Rat spermatogonial stem cells		(Liu et al., 2015)
Tris(*o*-methylphenyl) phosphate	TOCP	Neurotoxicity (o-TCP)	Various	Various		(Hendriks and Westerink, 2015)
Tris(*m*-methylphenyl) phosphate	No recent data					
Tris(*p*-methylphenyl) phosphate	No recent data					
Cresyl diphenyl phosphate	CDPhP	Acute toxicity	96h LC50 = 1,06 mg/L	*Danio rerio* embryo		(Du et al., 2015)
Cresyl diphenyl phosphate	CDPhP	Developmental toxicity	96h EC50 of pericardial edema = 0,38 mg/L	*Danio rerio* embryo		(Du et al., 2015)
Tri-n-butylphosphate	TBP / TnBP	Acute toxicity	96hLC50 = 7,82 mg/L	*Danio rerio* embryo		(Du et al., 2015)
Tri-n-butylphosphate	TBP / TnBP	Mortality	120hpf lowest effect level = 6.4E-4 µM	*Danio rerio* early life stage		(Noyes et al., 2015)
Tri-n-butylphosphate	TBP / TnBP	Long term toxicity	Long term NOEC = 1.3 mg/L	*Daphnia magna*	2	ECHA[b]
Tri-n-butylphosphate	TBP / TnBP	Short term toxicity	Short term EC50 = 68 mg/L	*Daphnia pulex*	2	ECHA[b]
Tri-n-butylphosphate	TBP / TnBP	Long term toxicity	Long term NOEC = 0.82 mg/L	*Oncorhynchus mykiss*	4	ECHA[b]
Tri-n-butylphosphate	TBP / TnBP	Short term toxicity	Short term EC50 = 11 mg/L	*Oncorhynchus mykiss*	4	ECHA[b]
Tri-n-butylphosphate	TBP / TnBP	Endocrine disruption	PXR agonistic activity, AR and GR antagonistic activity	Gene reporter assay		(Kojima et al., 2016)
Tri-n-butylphosphate	TBP / TnBP	Neurotoxicity	Altered expression of genes related to the nervous system	Embryo test with *Danio rerio*		(Sun et al., 2016b)
Tri-n-butylphosphate	TBP / TnBP	Developmental toxicity	Hatchability, gross abnormality rate, heart rate,	Embryo test with *Oryzias latipes*		(Sun et al., 2016a)
Tri-n-butylphosphate	TBP / TnBP	Developmental toxicity	Reduced average speed at 3125 µg/L	Embryo test with *Danio rerio*		(Sun et al., 2016b)
Tri-n-butylphosphate	TBP / TnBP	Developmental toxicity	96hEC50 of pericardial edema = 17,7 mg/L	*Danio rerio* embryo		(Du et al., 2015)
Tri-n-butylphosphate	TBP / TnBP	neurodevelopment	Pectoral fin	*Danio rerio* early life stage		(Noyes et al., 2015)
Tri-iso-butylphosphate	TBP / TiBP	Growth inhibition	Growth inhibition, EC50 = 34.1 mg/L	*Desmodesmus subspicatus*	2	ECHA[b]

Compound	Abbreviation	Effect type	Measured endpoint	Assay/species	Reliability[a]	Reference
Tri-iso-butylphosphate	TBP / TiBP	Short term toxicity	Short term EC50 = 5.8 mg/L	*Daphnia magna*	2	ECHA[b]
Tri-iso-butylphosphate	TBP / TiBP	Short term toxicity	Short term EC50 = 20 mg/L	*Oryzias latipes*	2	ECHA[b]
Triphenyl phosphate	TPP / TPHP	Mortality	120 hpf lowest effect level = 0.0064µM (0.002 mg/L)	*Danio rerio* 120 hpf		(Noyes et al., 2015)
Triphenyl phosphate	TPP / TPHP	Acute toxicity	96h LC50 = 1,53 mg/L	*Danio rerio* embryo		(Du et al., 2015)
Triphenyl phosphate	TPP / TPHP	Acute toxicity	96h LC50 = 1,026 mg/L	Adult *Danio rerio*		(Du et al., 2016)
Triphenyl phosphate	TPP / TPHP	Growth inhibition	Growth inhibition, NOEC = 2.5 mg/L	*Chlorella vulgaris*	2	ECHA[b]
Triphenyl phosphate	TPP / TPHP	Long term toxicity	Long term NOEC = 0.254 mg/L	*Daphnia magna*	2	ECHA[b]
Triphenyl phosphate	TPP / TPHP	Short term toxicity	Short term EC_{50} = 0.25 mg/L	*Gammarus pseudolimnaeus*	2	ECHA[b]
Triphenyl phosphate	TPP / TPHP	Short term toxicity	Short term EC_{50} = 0.3 mg/L	*Oncorhynchus mykiss*	2	ECHA[b]
Triphenyl phosphate	TPP / TPHP	Neurotoxicity	Various	Various		(Hendriks and Westerink, 2015)
Triphenyl phosphate	TPP / TPHP	Endocrine disruption (thyroid)	Increased T3 and T4 protein concentration and genes involved in thyroid hormone synthesis	*Danio rerio* larvae (7dpf)		(Kim et al., 2015)
Triphenyl phosphate	TPP / TPHP	Endocrine disruption (estrogen)	ER and PXR agonistic activity, AR and GR antagonistic activity	Reporter gene assay		(Kojima et al., 2016)
Triphenyl phosphate	TPP / TPHP	Endocrine disruption (estrogen)	Genes and proteins related to the HPG axis	*Danio rerio*		(Liu et al., 2016)
Triphenyl phosphate	TPP / TPHP	Endocrine disruption	decreased leydig cells and mild disorganization of Sertoli cells	male ICR mice (*Mus musculus*)		(Chen et al., 2015a)
Triphenyl phosphate	TPP / TPHP	Endocrine disruption	decreased testosterone levels and altered expression of genes related to T synthesis	murine Leydig cell line TM3		(Chen et al., 2015b)
Triphenyl phosphate	TPP / TPHP	Reproduction	Reproduction, lowest effect concentration = 6.30 µM (2.06 mg/L)	*C. elegans*		Behl et al., 2016
Triphenyl phosphate	TPP / TPHP	Neurodevelopment	Yolc sac edema (lowest effect level 64µM (21 mg/L)	*Danio rerio* 120 hpf		(Noyes et al., 2015)
Triphenyl phosphate	TPP / TPHP	Developmental toxicity	Hatchability, time to hatch, gross abnormality rate, heart rate, body length	Embryo test with *Oryzias latipes*		(Sun et al., 2016a)
Triphenyl phosphate	TPP / TPHP	Developmental toxicity	C. elegans larval development, point of departure = 0.9µM (0.29 mg/L)	*C. elegans*		(Behl et al., 2015)
Triphenyl phosphate	TPP / TPHP	Developmental toxicity	C. elegans larval development, lowest effective concentration = 0.16 µM (0.05 mg/L)	*C. elegans*		Behl et al., 2016
Triphenyl phosphate	TPP / TPHP	Developmental toxicity	Zebrafish embryonic development, point of departure = 2µM (0.65 mg/L)	*Danio rerio* embryo		(Behl et al., 2015)
Triphenyl phosphate	TPP / TPHP	Developmental toxicity	96h EC50 of pericardial edema = 0.64 mg/L	*Danio rerio* embryo		(Du et al., 2015)
Triphenyl phosphate	TPP / TPHP	Developmental neurotoxicity	Human neurite outgrowth, point of departure= 15,9 µM, cytotoxicity also occurring	Human neurons (hN2) cells		(Behl et al., 2015)

Compound	Abbreviation	Effect type	Measured endpoint	Assay/species	Reliability[a]	Reference
Triphenyl phosphate	TPP / TPHP	Behavior	Behavior in novel environment, startle habituation, social affiliation	*Danio rerio* early life stage		(Oliveri et al., 2015)
Triphenyl phosphate	TPP / TPHP	Oxidative stress	Enzyme activity and gene expression	male ICR mice (*Mus musculus)*		(Chen et al., 2015a)
Triphenyl phosphate	TPP / TPHP	Oxidative stress	enzyme activity and gene expression	murine Leydig cell line TM3		(Chen et al., 2015b)
Triphenyl phosphate	TPP / TPHP	Metabolic disruption/hepatic toxicity	Disruption of metabolism pathways	Adult *Danio rerio*		(Du et al., 2016)
Tris(2-ethylhexyl) phosphate	TEHP	Mortality	120hpf lowest effect level = 6.4 μM (2.8 mg/L)	*Danio rerio* 120 hpf		(Noyes et al., 2015)
Tris(2-ethylhexyl) phosphate	TEHP	Growth inhibition	Growth inhibition NOEC > 40 mg/L	*Desmodesmus subspicatus*	1	ECHA[b]
Tris(2-ethylhexyl) phosphate	TEHP	Growth inhibition	Growth inhibition EC_{50} > 40 mg/L	*Desmodesmus subspicatus*	1	ECHA[b]
Tris(2-ethylhexyl) phosphate	TEHP	Long term toxicity	Long term NOEC = 1 mg/L	*Daphnia magna*	2	ECHA[b]
Tris(2-ethylhexyl) phosphate	TEHP	Short term toxicity	Short term EC50 > 0.08	*Daphnia magna*	1	ECHA[b]
Tris(2-ethylhexyl) phosphate	TEHP	Short term toxicity	Short term EC50 > 100 mg/L	*Danio rerio*	2	ECHA[b]
Tris(*p*-tert-butylphenyl) phosphate	No recent data					
4-tert-Butylphenyl diphenyl phosphate	BPDP	Mortality	120 hpf lowest effect level = 0.064 μM (0.02 mg/L)	*Danio rerio* 120 hpf		(Noyes et al., 2015)
4-tert-Butylphenyl diphenyl phosphate	BPDP	Neurodevelopment	Delayed progression, yolc sac edema, axis, eyes, snout, jaw, pericardial edema, pectoral fin, caudal fin	*Danio rerio* early life stage		(Noyes et al., 2015)
4-tert-Butylphenyl diphenyl phosphate	BPDP	Developmental toxicity	C. elegans larval development, point of departure = 3.3μM (1.3 mg/L)	*C. elegans*		(Behl et al., 2015)
4-tert-Butylphenyl diphenyl phosphate	BPDP	Developmental toxicity	C. elegans larval development, lowest effective concentration = 2.5 μM (0.96 mg/L)	*C. elegans*		Behl et al., 2016
4-tert-Butylphenyl diphenyl phosphate	BPDP	Developmental toxicity	Zebrafish embryonic development, point of departure = 9,8μM (3.75 mg/L)	*Danio rerio* embryo		(Behl et al., 2015)
4-tert-Butylphenyl diphenyl phosphate	BPDP	Developmental neurotoxicity	Neuroprogenitor proliferation, point of departure = 7,2μM (2.75 mg/L), cytotoxicity also occurring	Human neuroprogenitor (hNP1) cells		(Behl et al., 2015)
4-tert-Butylphenyl diphenyl phosphate	BPDP	Developmental neurotoxicity	Rat neurite outgrowth, point of departure= 14,9μM (5.70 mg/L), cytotoxicity also occurring	rat primary cortical cultures		(Behl et al., 2015)

Compound	Abbreviation	Effect type	Measured endpoint	Assay/species	Reliability[a]	Reference
4-tert-Butylphenyl diphenyl phosphate	BPDP	Developmental neurotoxicity	Human neurite outgrowth, point of departure= 4,1 μM 1.57 mg/L), cytotoxicity also occurring	Human neurons (hN2) cells		(Behl et al., 2015)
4-tert-Butylphenyl diphenyl phosphate	BPDP	reproduction	Reproduction, lowest effective concentration = 16 μM (6.1 mg/L)	*C. elegans*		Behl et al., 2016
bis(t-butylphenyl) phenyl phosphate)		No recent data				
Triethyl phosphate	TEP	Acute toxicity	96h LC50 = 1,25*10^3 mg/L	*Danio rerio* embryo		(Du et al., 2015)
Triethyl phosphate	TEP	Growth inhibition	Growth inhibition EC_{10} = 127 mg/L	*Desmodesmus subspicatus*	1	ECHA[b]
Triethyl phosphate	TEP	Growth inhibition	Growth inhibition EC_{50} = 901 mg/L	*Desmodesmus subspicatus*	1	ECHA[b]
Triethyl phosphate	TEP	Long term toxicity	Long term NOEC = 31.6 mg/L	*Daphnia magna*	1	ECHA[b]
Triethyl phosphate	TEP	Short term toxicity	24h EC_{50} = 900 mg/L	*Daphnia magna*	2	ECHA[b]
Triethyl phosphate	TEP	Short term toxicity	96h LC_{50} = 2100-2400 mg/L	*Alburnus alburnus*	2	ECHA[b]
Triethyl phosphate	TEP	Developmental toxicity	96h-EC50 of pericardium edema = 1,24*10^3 mg/L	*Danio rerio*		(Du et al., 2015)
Butyl diphenyl phosphate	BDPP	No recent data				
Dibutyl phenyl phosphate	DBPP	No recent data				
Trixylyl phosphate	TXP	Growth inhibition	Growth inhibition NOEC = 0.112 mg/L	*Selenastrum capricornutum*	1	ECHA[b]
Trixylyl phosphate	TXP	Growth inhibition	Growth inhibition EC_{50} >1.011 mg/L	*Selenastrum capricornutum*	1	ECHA[b]
Trixylyl phosphate	TXP	Long term toxicity	Long term NOEC = 0.184 mg/L	*Chironomus plumosus*	2	ECHA[b]
Trixylyl phosphate	TXP	Short term toxicity	Short term EC_{50} = 0.060 mg/L	*Daphnia magna*	1	ECHA[b]
Trixylyl phosphate	TXP	Short term toxicity	96h LC50 > 1.119 mg/L	*Pimephales promelas*	1	ECHA[b]
Phenol, isopropylated, phosphate (3:1)	IPP	Mortality	120hpf lowest effect level = 0,0064 μM (IPP-2), 0.064 μM (IPP-3), 64 μM (IPP-1)	*Danio rerio* early life stage		(Noyes et al., 2015)
Phenol, isopropylated, phosphate (3:1)	IPP	Growth inhibition	Growth inhibition 72h NOEC = 0.31 mg/L	*Selenastrum capricornutum*	1	ECHA[b]
Phenol, isopropylated, phosphate (3:1)	IPP	Growth inhibition	Growth inhibition 75h EC50 > 2.5 mg/L	*Selenastrum capricornutum*	1	ECHA[b]
Phenol, isopropylated, phosphate (3:1)	IPP	Long term toxicity	Long term 21d NOEC = 0.006 for the product Kronitex 200	*Daphnia magna*	2	ECHA[b]
Phenol, isopropylated, phosphate (3:1)	IPP	Short term toxicity	Short term 48h EC50 > 1000	*Daphnia magna*	1	ECHA[b]
Phenol, isopropylated, phosphate (3:1)	IPP	Long term toxicity	Long term 30d NOEC = 0.024 for the product Kronitex 200	*Pimephales promelas*	2	ECHA[b]
Phenol, isopropylated, phosphate (3:1)	IPP	Short term toxicity	Short term 96h EC50 = 4.46	*Oncorhynchus mykiss*	2	ECHA[b]
Phenol, isopropylated, phosphate (3:1)	IPP	Neurodevelopment	Delayed progression, yolc sac edema, axis, pericardial edema, pectoral fin, caudal fin, touch responses	*Danio rerio* early life stage		(Noyes et al., 2015)

Compound	Abbreviation	Effect type	Measured endpoint	Assay/species	Reliability[a]	Reference
Phenol, isopropylated, phosphate (3:1)	IPP	Developmental toxicity	Mouse stem cell differentiation, point of departure = 66,1µM, cytotoxcitiy also observed	Mouse embryonic stem cells		(Behl et al., 2015)
Phenol, isopropylated, phosphate (3:1)	IPP	Developmental toxicity	C elegans larval development, point of departure = 3,2µM (1.45 mg/L)	*C. elegans*		(Behl et al., 2015)
Phenol, isopropylated, phosphate (3:1)	IPP	Developmental toxicity	C elegans larval development, lowest effective concentration = 1.60 µM (0.72 mg/L)	*C. elegans*		Behl et al., 2016
Phenol, isopropylated, phosphate (3:1)	IPP	Developmental toxicity	Zebrafish embryonic development, point of departure = 4,9µM (2.2 mg/L)	*Danio rerio* embryo		(Behl et al., 2015)
Phenol, isopropylated, phosphate (3:1)	IPP	Developmental neurotoxicity	Neuroprogenitor proliferation, point of departure = 8.7 µM, cytotoxicity also occurring	Human neuroprogenitor (hNP1) cells		(Behl et al., 2015)
Phenol, isopropylated, phosphate (3:1)	IPP	Developmental neurotoxicity	Rat neurite outgrowth, point of departure= 12.7 µM, cytotoxicity also occurring	rat primary cortical cultures		(Behl et al., 2015)
Phenol, isopropylated, phosphate (3:1)	IPP	Developmental neurotoxicity	Human neurite outgrowth, point of departure= 13.9 µM, cytotoxicity also occurring	Human neurons (hN2) cells		(Behl et al., 2015)
Phenol, isopropylated, phosphate (3:1)	IPP	reproduction	Reproduction, lowest effect concentration = 10 µM (4.5 mg/L)	*C. elegans*		Behl et al., 2016

[a] reliability categories: 1 – reliable without restrictions, 2 – reliable with restrictions, 3 – not reliable, 4 – not assignable
[b] ECHA – information found by cas search on https://echa.europa.eu/information-on-chemicals/registered-substances
[c] point-of departure (POD), defined as the lowest concentration where the response exceeds the THR (background noise level), and is calculated by linear interpolation between the two concentration points where their range of response includes the THR. In this study, the THR values were set as 20% (mouse embryonic stem cell differentiation), 35% (mouse embryonic stem cell viability), 15% (rat neurite outgrowth), 20% (rat neuron viability), 15% (human neurite outgrowth), 35% (human neuron viability), 20% (human neuroprogenitor cell proliferation), 20% (human neuroprogenitor cell viability), and 35% (rat neuron firing rate), 15% (C. elegans larval development), and 20% (zebrafish embryonic development and mortality) based on the assay-specific intrinsic DMSO control variability (Behl et al., 2015)