GREEN CHEMICAL DESIGN LIMITED

Report for pinfa:
Grouping of organophosphorus flame retardants in the context of REACH

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1. Executive summary

pinfa is engaged in all the issues arising from the EU's Chemical Strategy for Sustainability. One of them is the content of the draft Chemical Restriction roadmap. In this context where the Restrictions Roadmap under the Chemicals Strategy for Sustainability (CSS) has included a grouping approach to substances registered under the REACH Regulation. The recently published Commission working document includes reference to several types of flame retardant. Although the Organo Phosphorus Flame Retardants (OPFRs, often also "organophosphate flame retardants") are classified in accordance with the CLP Regulation, there are publications in the literature which link the complete group of OPFRs to health and environmental hazards.

Any grouping should be based on sound scientific methodology. Therefore, pinfa commissioned this study to elaborate whether structural similarities of OPFRs are also reflected in similar physico-chemical, toxicological or ecotoxicological properties and to what extent grouping can make sense in the context of what may arise from the CSS. The report does not examine regulatory activities beyond the REACH-compliant data sets, being technical in focus.

There is no solid basis for grouping all OPFRs, but based on structural features alone these structural groups can be identified:

Trialkylphosphates
Triarylphosphates
Monoalkyldiarylphosphates
Chloroalkylphosphates
Bisarylphosphates
Phosphonates
Miscellaneous (not considered in detail)

Detailed investigation shows that these structural groups have predictable trends in physico-chemical properties and reasonably consistent hazard profiles, although there can be differences within a structural group.

The set of OPFRs is data-rich in respect of the key REACH requirements and most weight of evidence should be given to those data, not to non-standard studies; there is no immediate or major need for collection of further data outside of the REACH data set. All conclusions are based on reliable Klimisch 1 and 2 OECD or comparable guideline studies from the REACH dossiers.

The main conclusions of the report are:

1. **OPFRs cannot be grouped together as one group** as this cannot be justified by conclusive scientific means following the basic rules for grouping and due to their different chemical structures, their different physical-chemical, their toxicological-, eco-toxicological and their environmental fate properties (based on reliable Klimisch 1 and 2 OECD or comparable guideline studies from the REACH dossiers).

2. Within groups of OPFRs based on structural features and physicochemical properties, the eco-toxicology is in line with the often-observed correlation between octanol-water partition coefficient and effect level. Each structural group has generally consistent toxicological hazard profiles; however, there can be substantial differences in toxicity, e.g. within the trialkylphosphates. Therefore, it is necessary to check whether to exempt certain products or subdivide structural groups further before considering regulatory measures on a (sub-)group.
3. Extrapolation from one group to another is neither feasible nor can it be justified by scientific means when comparing data available on the same endpoints on the substances of the other structural groups.

A glossary of terms not defined in the text is given in section 9.

2. Introduction

Purpose

The phosphorus, inorganic and nitrogen flame retardants association (pinfa), a sector group of Cefic, the European Chemical Industry Council, is engaged in all the issues arising from the EU Chemical Strategy for Sustainability. CARACAL has issued a Commission Staff Working Document, "Restrictions Roadmap under the Chemicals Strategy for Sustainability".[1] This roadmap seeks to enhance the restriction of hazardous chemicals, including the Grouping approach. Several halogenated Organo Phosphorus Flame retardants are included; certain NGOs are aiming at inclusion of non-halogenated ones into this group. . In the current proposal the flame retardants seem to be grouped on grounds of "functionality" rather than common chemistry or properties.

Grouping of substances and read-across is a commonly used approach for filling data gaps in registrations submitted under REACH. This approach uses relevant information from analogous ('source') substances to predict the properties of 'target' substances. If the grouping and read-across approach is applied correctly, experimental testing may be reduced, as there is no need to test every target substance. The grouping of substances and read-across approach needs to be adequately and appropriately documented. A robust scientific justification must be provided that fulfils the legal requirements However, for the OPFRs the amount of read-across in registration dossiers is small. The focus in this report is whether grouping for risk management is valid.

pinfa acknowledges that some grouping of hazardous chemicals is appropriate and potentially useful for all stakeholders, where justified scientifically. However, the way it is being proposed by some is non-scientific and misses the fact that there are great differences among the OPFRs , in chemical properties, toxicological and ecotoxicological profiles and uses and applications. Even within the structural group of halogenated OPFRs there is variation of properties.

Therefore, pinfa commissioned this study to elaborate whether structural similarities of REACH-registered OPFRs are also reflected in similar physico-chemical toxicological or ecotoxicological properties and to what extent grouping can make sense.

Peter Fisk of Green Chemical Design Limited has been asked by pinfa to prepare an expert scientific review for its consideration. This report represents his conclusions as a scientific expert on chemical regulation, based on data and input received from pinfa and some public sources.

Extent of literature review

The author conducted a basic review of scientific literature to search for prior art relevant to grouping. Search terms were around phosphate esters and toxicology. Approximately 18 papers and regulatory documents were assessed to be relevant to grouping of OPFRs and were reviewed for that purpose only, and these are not discussed in any depth here. A fuller review is not needed for the present purpose, since the basis of the report are the REACH registrations of the substances and are considered of high reliability. Furthermore, no sources were found which undermine that approach. For reasons of transparency, the list of sources is given in section 9. Consequently, this document must not be considered as an in-depth review of all the science.

[1] SWD(2022) 128 final, Brussels, 25.4.2022.

One group of OPFRs or one substance at a time?

The report examines fully the question of how many groups could be set up to describe the OPFRs. If more than one group is necessary scientifically, then the case to group all OPFRs is disproven. By contrast, the hypothesis that each substance must be dealt with one at a time can be discounted should reasonable groups be identified.

Overview of the remainder of the report

The approach is to set out the main information simply, with more detailed information found in annexes.

Based on chemical structure alone it is first set out that potential structural groups derived from the whole set of substances can be identified and justified based on physicochemical properties. The next stage is to examine whether:

- Is one group sufficient?
- Are structural groups homogeneous in respect of hazard?
- Are differences such that each substance must be dealt with in isolation?

It is important to note an important finding of this study, which is that all the REACH registration dossiers examined stand by themselves and are data-rich. The amount of read-across is limited to some supporting statements, so the discussion of grouping in this report does not impact upon the REACH registrations.

The substances listed by pinfa

pinfa has provided to Peter Fisk:

1. Two spreadsheets of substance information to be included in the work, with (limited) use and classification information.
2. Chemical Safety Reports (CSRs) for individual OPFRs which are part of the REACH registrations.

The substances included by pinfa are listed below in three tables, divided (for clarity) into three types by the author, in CAS number order for each type. In Annex 3 the substances are shown with graphics of the structures.

Phosphate esters

This list includes the chlorinated phosphate esters that have already been grouped by ECHA; they are useful to include here for purposes of comparison.

Table 1: Phosphate esters

Name	Known as	CAS number	EC number
Triethyl phosphate	TEP	78-40-0	201-114-5
Tris-(2-ethylhexyl) phosphate	TEHP	78-42-2	201-116-6
Tris(butoxyethyl) phosphate	TBEP	78-51-3	201-122-9
Triphenyl phosphate	TPP	115-86-6	204-112-2
Tris(2-chloroethyl) phosphate	TCEP	115-96-8	204-118-5
Tri n-butyl phosphate	TBP	126-73-8	204-800-2
Diphenyl (2-ethylhexyl) phosphate	EHDP	1241-94-7	214-987-2
Tris(methylphenyl) phosphate* (low ortho- substitution)	TCP	1330-78-5	809-930-9
Tris(2-chloro-1-methylethyl) phosphate*	TCPP	13674-84-5 1244733-77-4	237-158-7
Tris[2-chloro-1-(chloromethyl)ethyl] phosphate	TDCP	13674-87-8	237-159-2
Trixylyl phosphate* ***	TXP	25155-23-1	246-677-8
Cresyl diphenyl phosphate*	CDP	26444-49-5	247-693-8
Alkyl diphenyl phosphate* (ECHA states this to be dodecyl)	ADP	27460-02-2	431-760-5
Isodecyl diphenyl phosphate	IDDP	29761-21-5	249-828-6
Resorcinol bis (diphenyl phosphate)*	RDP	57583-54-7	260-830-6 701-337-2
Isopropylated triphenyl phosphate*	IPP	68937-41-7	273-066-3
Bisphenol-A bis(diphenyl phosphate) [Phosphoric trichloride, reaction products with 4,4'-isopropylidenediphenol and phenol]	BDP	181028-79-5, 5945-33-5	425-220-8
Butylated triphenyl phosphate	BPDP	220352-35-2	700-990-0 939-505-4
Oligomeric ethyl ethylene phosphate**		184538-58-7	606-033-2
Mixtures of esters of phosphoric acid**		1003300-73-9	

*multi-constituent; **UVCB; not discussed further herein; *** TXP is not used as a flame retardant as such, but is a fire resistant hydraulic fluid

Other substances that are not part of this study but for which there is some literature data can include pure constituents of some of the above, where they are multi-constituent.

Phosphonate esters

Table 2: Phosphonate esters

Name	Known as	CAS number	EC number
Diethyl ethyl phosphonate	DEEP	78-38-6	201-111-9
Dimethyl methyl phosphonate	DMMP	756-79-6	756-79-6
Diethyl bis(hydroxyethyl) aminomethylphosphonate		2781-11-5	220-482-8
Dimethyl propane phosphonate	DMPP	18755-43-6	242-555-3

Others, non-phosphate esters and non-phosphonate esters

Table 3: Miscellaneous substances

Name	Known as	CAS number	EC number
Ethylenediamine-o-phosphate	EDAP,	14852-17-6	283-914-9
9,10-Dihydro-9-oxa-10-phosphaphenanthren-10-oxide	DOPO	35948-25-5	252-813-7
Polyphosphonate homopolymer		68664-06-2	
Polycarbonate-Polyphosphonate copolymer		77226-90-5	
Diethylphosphinate, aluminium salt	DEPAL, Alpi	225789-38-8	428-310-5

3. Methods

Structural features

The main structural features included in the work are the number of phosphorus atoms in a molecule, and the pattern of the alkyl and aryl groups attached to phosphorus and oxygen.

Descriptors

The molecular descriptors included in the review of grouping include:

- Molecular weight
- Physicochemical properties such as octanol-water partition coefficient
- Solubility properties such as solubility in water and Hansen Solubility Parameters (HSP), which describe fundamental intermolecular energies.
  HSP values describe how cohesive energy of a molecule in solution can be quantified in terms of a solubility parameter broken down into three terms: dispersion, polarity and hydrogen bonding. These are referred to as δD, δP and δH.

Classifications and hazard

The normal human health and environmental classifications are considered. Other hazardous properties that do not lead to formal classification have also been examined.

Uses

The end uses of the substances could be relevant but are not considered in this report. Most of the substances listed are flame retardants but some have other uses.

Some publications discuss the amounts of OPFRs that can be found in the environment. The fact that OPFRs can be found is not unexpected, given their use pattern. Their presence in the environment can be rationalised – and modelled quantitatively - on the basis of in-service losses from polymers (diffusion over many years from the bulk of a plastic to its surface, followed by loss to the environment). Presence in the environment should be subject to risk assessment for the environment and human health. That is not discussed herein: the primary focus is on hazard and how that relates to possible structural groups.

Properties that will be considered for possible structural groups

These are:

- Physicochemical properties in general including Hansen Solubility parameters (HSP; see Annex 1, which explains their technical basis).
- Environmental fate
- Ecotoxicology.
- Mammalian toxicology
- Genotoxicity

4. Information sources

Chemical Safety Reports

REACH Chemical Safety Reports (CSRs) or previous high-level documents such as pre-REACH regulatory risk assessments were available for most substances.

Sources search

Investigation of the possibility of new information outside the CSRs was made[2]. Sources examined were:

- The ECHA web site;
- The PubChem database;
- Internet searching of published papers concerned with phosphate ester toxicology reviews; a selection of the papers of interest found were downloaded and read (see section 9).

Data sources are CSRs unless stated otherwise.

The EPIWEB database and QSAR software was used to obtain results for endpoints where more information was needed (tabulated in Annex 2).

[2] CSRs are updated periodically and do refer to wider literature where necessary.

5. Findings for phosphate esters

It should be noted that this document is not a review of all the data present in the REACH dossiers, but examines the data in a way sufficient to explore the grouping issue. Neither is it intended to be a comprehensive overview of phosphate esters. It does achieve one very important finding: there are structural groups in terms of the important health and ecotoxicological endpoints, thereby disproving that one group of OPFRs exists.

Molecular descriptors and the structural groups present

The substances' Hansen Solubility Parameters (HSP) values were calculated. The HSP and other molecular descriptors for the OPFRs are tabulated in Annex 1, along with a more detailed description of what the parameters signify. This Annex suggests that HSP are a powerful way of understanding the substances; see Figure 1 below which shows how the groups are formed in HSP property space. There are many kinds of molecular descriptor in chemical science; HSP values are readily available and easily understood so are particularly useful; no claim is made here that they are the best possible approach, but they are very useful here, and are very readily understood and accessed.

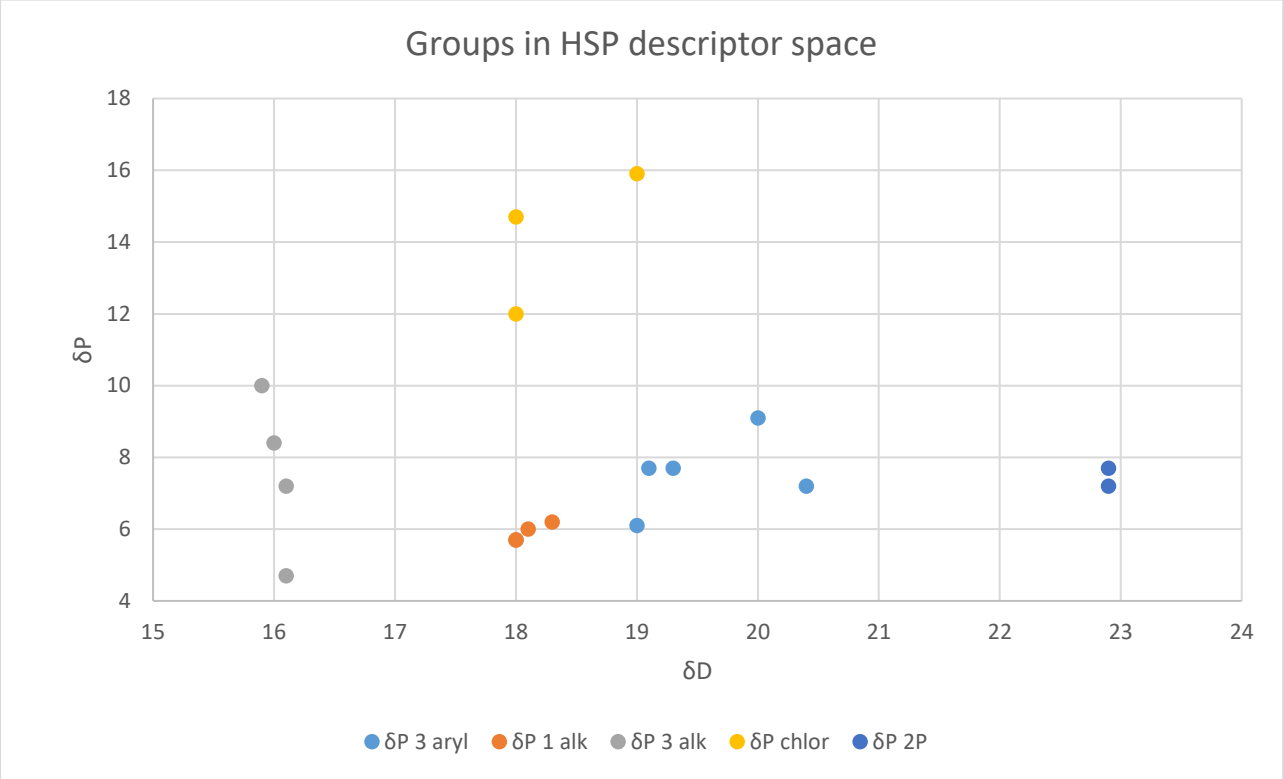
The HSP values were calculated ones because few measured ones were available for this set, but the values are reliable. It was observed that the dispersion (δD) and polarity (δP) properties varied, but the hydrogen bonding energy varied very little so that is not used further herein. HSP values relate directly to fundamental molecular properties in respect of absolute intermolecular energies.

On the basis of chemical structure and the HSP values, five structural groups were identified. HSP values show good grouping and separations.

δP values for various structural types are plotted against δD; the structural groups identified were substances with various attachments to the P=O group:

Three aryl rings	- δP 3 aryl in the graph
Two aryl rings, one alkyl chain	- δP 1 alkyl
Three alkyl chains	- δP 3 alk
Three chloroalkyl chains	- δP chlor
Two P atoms, various	- δP 2P

Figure 1: Grouping of phosphate esters from structure and HSP values



It is seen that the five structural groups separated well in HSP descriptor space, covering a substantial range of that space[3], with each structural groups' members well clustered together. This analysis confirms that the concept of dividing the substances based on the structural features present is a sound method, because the structural groups are based on fundamental chemical properties. It must also be noted that the range of δD and δP values is wide – therefore these are energetically-significant separations in terms of intermolecular forces.

It is relevant to point out that the usual physicochemical properties would not produce such a useful grouping, as is exemplified in the next section.

The health and ecotoxicological classifications are discussed in Annex 2.

Next stage of review

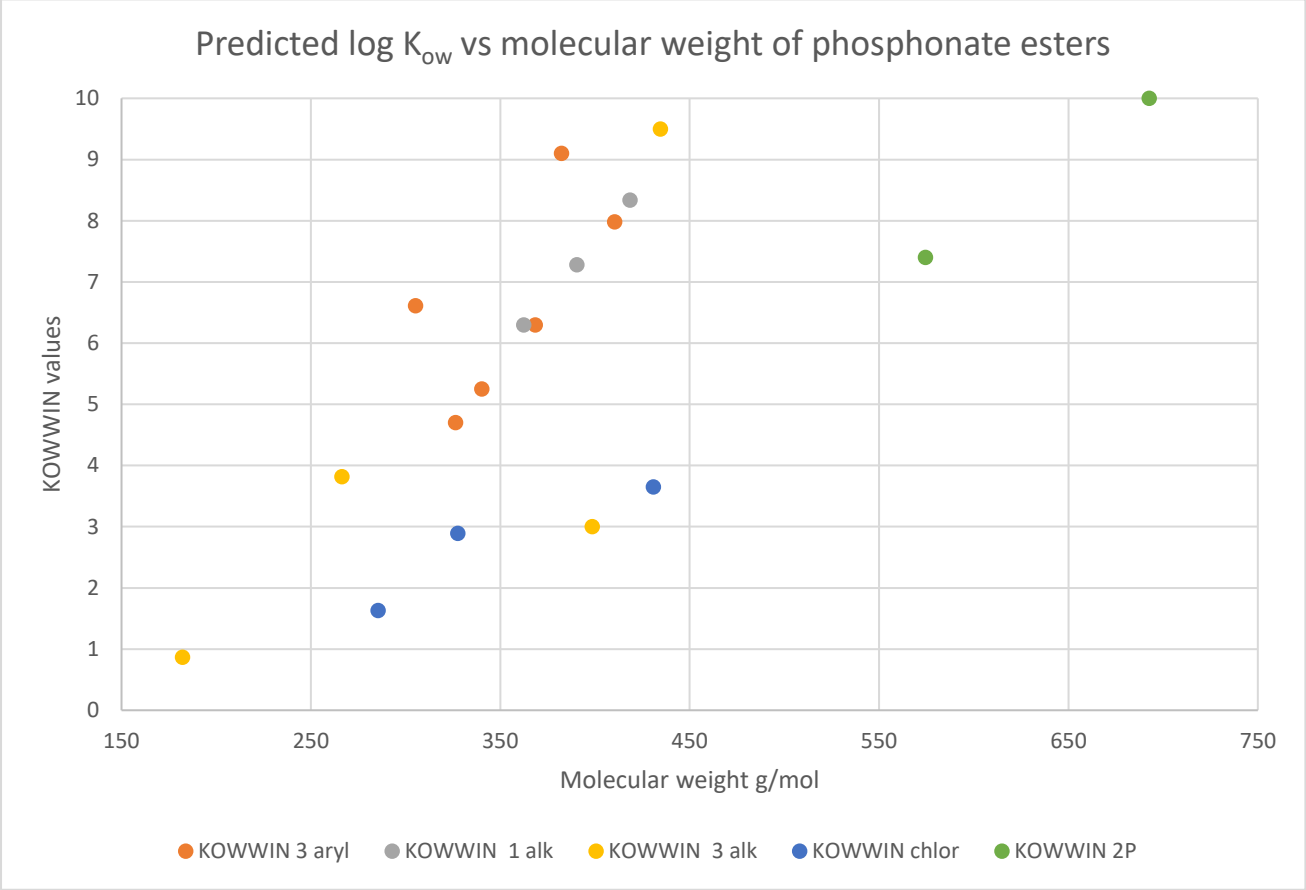
Having established that structural groups can be identified, it is necessary to examine their homogeneity in respect of properties.

Physicochemical properties

Annex 2 gives the full list investigated. As an important example of some key data, the log octanol-water partition coefficient (log K_{ow}). has been examined This parameter is widely used as an indicator of uptake into organisms, is a REACH requirement and an obvious property for study in this context. As tabulated in Annex 2, predicted values (KOWWIN method) have been used.

[3] Annex 1 gives more explanation.

Figure 2: Possible grouping of phosphate esters from K_{ow} and molecular weight



The general correlation of log K_{ow} with molecular weight is to be expected. However, there is no useful separation between structural types, so log K_{ow} is not useful for the purpose of identification of structural groups. The graph does usefully show that the range of these properties for OPFRs is wide, which helps to support the proposal of looking at these properties.

Environmental properties

Annex 2 gives the full list investigated.

Following on from the discussion of octanol-water partition coefficient above, it is important to examine the relationship of the aquatic ecotoxicology to log K_{ow}.

The predicted long-term NOEC values were obtained from ECOSAR; log NOEC is a linear function of log K_{ow}. It is however constructive to examine the measured vs predicted in more detail. This is shown in Annex 2, and it is concluded that measured and predicted values are in good agreement. Of practical relevance is to show environmental classification compared to K_{ow}. The predicted log K_{ow} (KOWWIN model) is used as an input to the QSAR, because this is a more consistent approach than the measured values[4].

In the comparison of the property data with the structural groups of substances, several observations can be made:

[4] That is a sound strategy for a series of related substances under review, when the measurements have been made in different laboratories using different methods.

- The aquatic ecotoxicology shows that invertebrates are usually the most sensitives species. The trend in the NOEC values follows the usual relationship to log K_{ow}, but at very high values of log K_{ow} no effects are seen due to the lack of solubility in water. The substances with classification for environmental properties can be compared to the log K_{ow}, as follows (Table 5).

- Generally hydrolysis rates are very low; slow hydrolysis has been demonstrated for some triaryl substances; these are likely to be the most labile because phenols are better leaving groups than alcohols[5].

- Biodegradation (Table 12a) seems to be rapid for substances which possess unbranched alkyl groups or aryl groups so long as the ring is not highly substituted. However, it may be that for a few substances the presence of triphenyl phosphate as a high solubility readily biodegradable constituent may be important[6].

None of these observations has strong relevance to the topic of grouping.

[5] These are reaction products.
[6] Communication from pinfa.

Table 5: Phosphate ester environmental classification and log K_{ow}

Sorted by log K_{ow}.

Name		CAS number	EC Number	KOWWIN	Environmental classification
Triethyl phosphate	TEP	78-40-0	201-114-5	0.87	
Tris(2-chloroethyl) phosphate	TCEP	115-96-8	205-118-5	1.63	H411
Tris(2-chloro-1-methylethyl) phosphate	TCPP	1244733-77-4 EC 807-935-0	237-158-7	2.89	
Tris(butoxyethyl) phosphate	TBEP	78-51-3	78-51-3	3	
Tris[2-chloro-1-(chloromethyl)ethyl] phosphate	TDCP	13674-87-8	237-159-2	3.65	H410
Tri-n-butyl phosphate	TBP	126-73-8	126-73-8	3.82	
Triphenyl phosphate	TPP	115-86-6	204-112-2	4.7	H400, H410
Cresyl diphenyl phosphate	CDP		945-730-9	5.25	H400, H412
Diphenyl (2-ethylhexyl) phosphate	EHDP	1241-94-7	214-987-7	6.3	
Tris(methylphenyl) phosphate	TCP	1330-78-5	809-930-9	6.3	H400, H410, 1
Butylated triphenyl phosphate (high TPP) Butylated triphenyl phosphate (low TPP)			700-990-0 939-505-4	6.61	H411 No classification
Isodecyl diphenyl phosphate	IDDP	29761-21-5		7.28	H413 ??
Resorcinol bis (diphenyl phosphate)	RDP		701-337-2	7.4	Not classified
Trixylyl phosphate	TXP	25155-23-1	246-677-8	7.98	H400, H410, H411,
Alkyl diphenyl phosphate		27460-02-2	431-760-5	8.34	H412
Isopropylated triphenyl phosphate	IPP	68937-41-7	273-066-3	9.1	H410,
Tris-(2-ethylhexyl) phosphate	TEHP	78-42-2	201-166-6	9.5	
Bisphenol-A bis(diphenyl phosphate)	BDP	181028-79-5, 5945-33-5	425-220-8	10	

The ECOSAR model predictions have used the predicted KOWWIN values as inputs to the quantitative structure-activity relationships. This has been done to provide a uniform basis of comparison, and because measurement of octanol-water partition coefficient is particularly difficult for very hydrophobic substances, which applies to many of the substances in this study.

Human health properties

As an introduction the health-related classifications are now tabulated, as extracted from Table 13.

Table 6: Phosphate ester classifications for human health

Name	CAS number	EC number	Classification	Source
Diphenyl (2-ethylhexyl) phosphate	1241-94-7	214-987-2	No data	ECHA database
Alkyl diphenyl phosphate	27460-02-2	431-760-5	H315	PubChem
Isodecyl diphenyl phosphate	29761-21-5	249-828-6	Not classified	pinfa ECHA database
Triethyl phosphate	78-40-0	201-114-5	H302, H319	ECHA database
Tris-(2-ethylhexyl) phosphate	78-42-2	201-116-6	H315, H319	ECHA database
Tris(butoxyethyl) phosphate	78-51-3	201-122-9	H315	PubChem
Tri-n-butyl phosphate	126-73-8	204-800-2	H351, H302, H315	ECHA database
Triphenyl phosphate	115-86-6	204-112-2	Not classified	ECHA database
Tris(methylphenyl) phosphate	1330-78-5	809-930-9	H361	ECHA database
Trixylyl phosphate	25155-23-1	246-677-8	H360F,H373, H319	ECHA database
Cresyl diphenyl phosphate	26444-49-5	247-693-8	NC	pinfa
Isopropylated triphenyl phosphate	68937-41-7	273-066-3	H361, H373,	ECHA database
Butylated triphenyl phosphate	220352-35-2	606-905-2	Not classified	ECHA database
tris(2-chloroethyl) phosphate	115-96-8	204-118-5	H351, H360F, H302	ECHA database
tris(2-chloro-1-methylethyl) phosphate	13674-84-5	237-158-7	H302	ECHA database
tris[2-chloro-1-(chloromethyl)ethyl] phosphate	13674-87-8	237-159-2	H351	ECHA database

Name	CAS number	EC number	Classification	Source
Resorcinol bis (diphenyl phosphate)	57583-54-7	260-830-6	Not classified	ECHA database
Bisphenol-A bis(diphenyl phosphate)	181028-79-5, 5945-33-5	425-220-8	Not classified	ECHA database
Mixtures of esters of phophoric acid	1003300-73-9		Not classified	ECHA database
Oligomeric ethyl ethylene phosphate	184538-58-7	606-033-2	Not classified	ECHA database

The following generalisations about the structural groups can be made:

The oral repeated dose NOAEL values are relatively unremarkable, showing typical responses in organs such as the liver without any values showing high specific sensitivities. Therefore, these are not discussed further.

Carcinogenicity and fertility studies are the ones of most interest. See Table 7 below.

Neurotoxicity is included due to there being several published papers discussing this topic. It is beyond the scope of this document to review all published papers around OPFRs. However, studies with zebrafish larvae have attracted attention as a potential screen for neurotoxicity. This is important given that there is a superficial resemblance between OPFRs and substances which affect the nervous system. A literature review has shown serious inconsistencies in the published data sets. Therefore, a larger study of the non-standard sources could be needed, but not for the present document. There are *in vivo* neurotoxicity studies available for several of the OPFRs; no adverse effects are reported.

Table 7: Phosphate ester key health effects

Sub-group	Carcinogenicity	Mutagenicity	Fertility	Developmental	Neurotoxicity
Alkyl phosphates	One substance classified although effects are not pronounced.	Negative *in vitro* and *in vivo* for all substances.	Limited data, no effects	Studies available for all substances, no significant or classifiable effects.	Limited data, no effects
Alkyl aryl phosphates	***No data.***	Negative *in vitro* for all substances and *in vivo* for those tested.	Limited data		No effects observed
Triaryl phosphates	Limited data	One positive *in vitro* result, all negative *in vivo.*	**Classifiable effects for several substances**		No effects except for one ortho-substituted substance.
Chloroalkyl phosphates	**Classifiable effects**	Some positive *in vitro* results, all negative *in vivo.*	No effects		No effects
Phosphates with two P atoms	***No data***	Negative *in vitro* for both substances and *in vivo* for one tested.	No effects		Limited data, no effects

There are insufficient direct studies of endocrine system effects to draw any conclusions, and no clear effects are identified. However, developmental and repeated dose studies do not suggest strong endocrine effects.

For fertility effects, although the triaryls seem to have issues for several members of the sub-group, that is not seen for monoalkyl diaryls or other structural groups – the alkyl substitution makes a difference.

For carcinogenicity, the trialkyl sub-group has one classifiable substance but there are no other substances of concern; possibly the linear alkyl group is important, along with high bioavailability. The chloroalkyls all show effects, to differing degrees. This also could be associated with reactivity.

The conclusion in respect of the concerns of this report is that although classifiable effects for human health are seen, the whole set of OPFRs should not be treated as a single group because the structural groups have clearly differentiated patterns of effects and lack of effects.

Overall conclusions for phosphate esters

The main findings:

- Phosphate esters can be put into structural groups based on chemical structure and are separated well by use of the Hansen Solubility Parameters; these structural groups are generally consistent in respect of hazardous properties, although high level data are not available for every substance.
- Although octanol-water partition coefficient is not useful for grouping, it is useful in respect of ecotoxicity hazard; some substances with high log Kow do show classifiable properties.
- Ready biodegradation is found for some substances, and possible structural alerts can be seen, but does not impact significantly on grouping.
- Hydrolysis rate is slow or negligible and does not add any particular insights into grouping.
- Some structural groups show clear toxicological properties that require classification.

Section 8 brings the conclusions together.

6. Findings for phosphonate esters

Phosphonate esters contain a carbon to phosphorus bond and that makes them different to phosphate esters. Data for the small group of non-polymeric phosphonate esters are given in Annex 2. In addition to the difference in chemical structure, the group is found in HSP space in a different place to all the phosphate esters.

From this initial examination it seems that phosphonates could be grouped together but not with phosphates. It is arguable that the phosphonate with a diethanolamine moiety is different in HSP and physicochemical properties from the others, but there is only one example.

Conclusions for phosphonate esters

- The phosphonate esters in the study are all close in structure, of low molecular weight and highly water-soluble. Therefore, the conclusions drawn are necessarily narrower in applicability than for the phosphate esters, which cover more structural types and range.
- It is reasonable to consider that all four substances could be grouped together, although diethyl bis(hydroxyethyl) aminomethylphosphonate has a less complete data set.
- Degradation properties in general are similar (low biodegradation and slow hydrolysis).
- Three of the four examples have classifiable effects for fertility, but that is unlikely to be due to a mechanism common with the triaryl phosphates, which have that property. It suggestive of a specific reactive mechanism rather than any general interaction.

7. Findings for other substances (non-phosphates and non-phosphonate esters)

Five other substances have been listed by pinfa.

In summary, of the pinfa substances there is a salt of an amine, an aluminium salt of a phosphine, a cyclic phosphine and two polymers which have one monomer in common but not the other monomer. Each substance must therefore be treated individually because at the most fundamental level (structure) they are different from the other substances discussed in this report.

8. Overview of the conclusions

This report shows that there are structural groups of OPFRs based on structural features and physicochemical properties. These structural groups[7] are:

Trialkylphosphates
Triarylphosphates
Monoalkyldiarylphosphates
Chloroalkylphosphates
Bisarylphosphates
Phosphonates
Miscellaneous (not considered in detail).

The stepwise methodology used was:

- Collect physicochemical, environmental and health data from REACH registration sources or reliable published sources where necessary
- Examine the possibility of any coherent grouping in the largest science-based groups possible; those groups are derived on the basis of all of the hazard-related registration data[8].

The OPFRs subject to this study are data-rich in respect of the key requirements of the REACH Regulation and most weight of evidence should be given to those data, not to non-standard (and non-guideline) studies as often cited in publication found in the literature.

The main conclusions of the report are:

1. **OPFRs cannot be grouped together as one group** as this cannot be justified by conclusive scientific means following the basic rules for grouping and due to their different chemical structures, their different physical-chemical, their toxicological-, eco-toxicological and their environmental fate properties (based on reliable Klimisch 1 and 2 OECD or comparable guideline studies from the REACH dossiers).
2. Within groups of OPFRs based on structural features and physicochemical properties, the eco-toxicology is in line with the often-observed correlation between octanol-water partition coefficient and effect level. Each structural group has generally consistent toxicological hazard profiles; however, there can be substantial differences in toxicity, e.g. within the trialkylphosphates. Therefore, it is necessary to check whether to exempt certain products or subdivide structural groups further before considering regulatory measures on a (sub-)group.
3. Extrapolation from one group to another is neither feasible nor can it be justified by scientific means when comparing data available on the same endpoints on the substances of the other structural groups.

[7] Note that no examples of monoaryldialkylphosphates were in the pinfa data set.
[8] Non-standard data from the scientific literature have not been considered.

9. Glossary of terms and published sources

Table 8: Important terms and acronyms

Term or acronym	Definition
CARACAL	Competent Authorities for REACH and CLP (CARACAL): an expert group which advises the European Commission and ECHA on questions related to REACH and CLP.
CAS number	Chemical Abstracts Service substance code
Chemical Safety Report	An in-depth report that forms part of a REACH registration, covering properties and uses.
Classification H302 H315 H319 H351 H360 H361 H373 H400 H410 H411 H412	Hazards are described with an internationally agreed method: Harmful if swallowed Causes skin irritation Causes serious eye irritation Suspected of causing cancer May damage fertility or the unborn child Suspected of damaging fertility or the unborn child Causes damage to organs through prolonged or repeated exposure Very toxic to aquatic life Very toxic to aquatic life with long lasting effects Toxic to aquatic life with long lasting effects Harmful to aquatic life with long lasting effects.
CLP	Regulation on Classification, Labelling and Packaging of Substances and Mixtures
EC number	European Union substance code
EC10	Calculated 10% effect concentration
ECHA	European Chemicals Agency
ECOSAR	Software for estimation of effects on aquatic organisms based on the chemical structure
EPIWEB	Estimation programs Interface QSAR software package.
Not classified	Not classified
NGO	Non-governmental organisation
NOAEL	No adverse effect level
NOEC	No observed effect concentration
PubChem	A database of chemical properties.
QSAR	Quantitative structure-activity relationship
REACH	Registration, evaluation and authorisation of chemicals
UVCB	Unknown, variable composition or biological substance.

Published scientific papers that have been examined in this work are listed below.

Alzualde A, Behl M, Sipes NS, HsiehJ-H, Alday A,Tice RR,etal.2018.Toxicity profiling of flame retardants in zebrafish embryos using a battery of assays for developmental toxicity, neurotoxicity, cardiotoxicity and hepatotoxicity toward human relevance. Neurotoxicol Teratol70:40–50, PMID: 30312655, https://doi.org/10.1016/j. ntt.2018.10.002.
Behl, Mamta. Jui-Hu, Hsieh. Timothy J.Shafer, William R.Mundy, Julie R.Rice, Windy A. Boyd, Jonathan H. Freedman, E. Sidney Hunter III, Kimberly A. Jarema, Stephanie Padilla, Raymond R.Tice. Use of alternative assays to identify and prioritize organophosphorus flame retardants for potential developmental and neurotoxicity. Neurotoxicology and Teratology, Volume 52, Part B, November–December 2015, Pages 181-193.

Arlene Blum, Mamta Behl, Linda S. Birnbaum, Miriam L. Diamond, Allison Phillips, Veena Singla, Nisha S. Sipes, Heather M. Stapleton, and Marta Venier. Organophosphate Ester Flame Retardants: Are They a Regrettable Substitution for Polybrominated Diphenyl Ethers? Environ. Sci. Technol. Lett. 2019, 6, 638-649.

Committee to Develop a Scoping Plan to Assess the Hazards of Organohalogen Flame Retardants; Board on Environmental Studies and Toxicology; Division on Earth and Life Studies; National Academies of Sciences, Engineering, and Medicine. A Class Approach to Hazard Assessment of Organohalogen Flame Retardants (2019). Washington, DC: The National Academies Press. https://doi.org/10.17226/25412.

Dishaw LV, Hunter DL, Padnos B, Padilla S, Stapleton HM. Developmental exposure to organophosphate flame retardants elicits overt toxicity and alters behavior in early life stage zebrafish (Danio rerio). Toxicol. Sci. 2014a; 142:445–454. [PubMed: 25239634]

Du, Zhongkun, Guowei Wang, Shixiang Gao, Zunyao Wang. Aryl organophosphate flame retardants induced cardiotoxicity during zebrafish embryogenesis: By disturbing expression of the transcriptional regulators. Aquatic Toxicology 161, 2015, 25-32.

Glazer L, Hawkey AB, Wells CN, Drastal M, Odamah K-A, BehlM, etal. 2018. Developmental exposure to low concentrations of organophosphate flame retardants causes lifelong behavioral alterations in zebrafish. Toxicol Sci 165(2):487–498, PMID: 29982741, https://doi.org/10.1093/toxsci/kfy173.

Gu, Yuxin, Yu Yang, Bin Wan, Minjie Lic, Liang-Hong Guo. Inhibition of O-linked N-acetylglucosamine transferase activity in PC12 cells – A molecular mechanism of organophosphate flame retardants developmental neurotoxicity. Biochemical Pharmacology, Volume 152, June 2018, Pages 21-33.

Jarema, Kimberly A., Deborah L. Hunter, Rachel M. Shaffer, Mamta Behl, and Stephanie Padilla. Acute and developmental behavioral effects of flame retardants and related chemicals in zebrafish. Neurotoxicol Teratol. 2015; 52(0 0): 194–209

McGee SP, Konstantinov A, Stapleton HM, Volz DC. Aryl phosphate esters within a major PentaBDE replacement product induce cardiotoxicity in developing zebrafish embryos: potential role of the aryl hydrocarbon receptor. Toxicol. Sci. 2013; 133:144–156. [PubMed: 23377616]

Noyes, Pamela D., Derik E. Haggard, Greg D. Gonnerman, and Robert L. Tanguay. Advanced Morphological — Behavioral Test Platform Reveals Neurodevelopmental Defects in Embryonic Zebrafish Exposed to Comprehensive Suite of Halogenated and Organophosphate Flame Retardants. Toxicological Sciences, 145(1), 2015, 177–195

Oliveri AN, Bailey JM, Levin ED. 2015. Developmental exposure to organophosphate flame retardants causes behavioral effects in larval and adult zebrafish. Neurotoxicol Teratol 52(ptB):220–227, PMID: 26344674, https://doi.org/10.1016/j. ntt.2015.08.008.

Patisaul, Heather B., Mamta Behl, Linda S. Birnbaum, Arlene Blum, Miriam L. Diamond, Seth Rojello Fernández, Helena T. Hogberg, Carol F. Kwiatkowski, Jamie D. Page, Anna Soehl, and Heather M.Stapleton. Beyond Cholinesterase Inhibition: Developmental Neurotoxicity of Organophosphate Ester Flame Retardants and Plasticizers. Environmental Health Perspectives, 129 (10) 2021.

Shi Q, Wang M, Shi F, Yang L, Guo Y, Feng C, etal. 2018. Developmental neurotoxicity of triphenylphosphate in zebrafish larvae. Aquat Toxicol 203:80–87, PMID: 30096480, https://doi.org/10.1016/j.aquatox.2018.08.001.

Sun L, Xu W, Peng T, Chen H, Ren L, Tan H, etal. 2016. Developmental exposure of zebrafish larvae to organophosphate flame retardants causes neurotoxicity. Neurotoxicol Teratol55:16–22, PMID: 27018022, https://doi.org/10.1016/j.ntt. 2016.03.003.

Wei, Gao-Ling, Ding-Qiang Li, Mu-Ning Zhuo, Yi-Shan Liao, Zhen-Yue Xie, Tai-Long Guo a, Jun-Jie Li, Si-Yi Zhang, Zhi-Quan Liang. Organophosphorus flame retardants and plasticizers: Sources, occurrence, toxicity and human exposure. Environmental Pollution 196 (2015) 29e46

Yang, Jiawen, Yuanyuan Zhao, Minghao Li, Meijin Du, Xixi Li and Yu Li. A Review of a Class of Emerging Contaminants: The Classification, Distribution, Intensity of Consumption, Synthesis Routes, Environmental Effects and Expectation of Pollution Abatement to Organophosphate Flame Retardants (OPFRs) Int. J. Mol. Sci. 2019, 20, 2874.

Zhang, S., D. Ireland, N. S. Sipes, M. Behl, and Eva-Maria S. Collins. (2019). "Screening For Neurotoxic Potential Of 15 Flame Retardants Using Freshwater Planarians". Neurotoxicology And Teratology. Volume 73, 54-66.

10. Annex 1: Molecular descriptors

Simple molecular descriptors are tabulated below. Included there are values for Hansen Solubility parameters, which help to confirm the structural groups proposed as described in Annex 2.

Hansen Solubility Parameters

Many chemists have found these parameters to be very useful in the understanding of intermolecular interactions relevant to desired performance; see https://www.hansen-solubility.com/HSPiP/

They are also relevant to hazardous properties.

For an introduction go to https://www.hansen-solubility.com/HSP-science/basics.php which describes how cohesive energy of a molecule in solution can be described in terms of a solubility parameter broken down into three terms: dispersion, polarity and hydrogen bonding. These are referred to as δD, δP and δH.

Values of these properties for many molecules have been measured and can be calculated for others.

HSP were originally developed as a method to explore solubility properties of polymers but since then they have been found to be useful for solubility in general and then have been applied to a wide range of other chemical phenomena involving interactions between molecules.

Applicability to regulatory issues

The starting point is to consider uptake into cells. In its simplest expression, uptake of a substance from an aqueous environment into an organism can be related to the relative affinity of a molecule for water and the lipids, proteins and membranes which the organism consists of. Therefore, it can easily be imagined that, high dispersion energy (δD), might relate to van der Waals' bonding to non-polar substrates, and hydrogen bonding will relate to affinity to water (δH). Additionally, strong polar interactions with proteins found in cells and cellular membranes will be expressed in δP.

It is interesting to note that HSP are under investigation by other workers as useful predictors of skin and eye irritation, exposure situations where the solubility and permeability of a tissue triggers such local effects.

However, systemic toxic effects depend on the bioavailability and the metabolic path of the molecule. Any possible link between HSP and the *in vivo* metabolism of chemicals has not been examined yet and this is where HSP may have limitations.

Shortcomings of current methods to study uptake

Why is there any need to examine HSP? Is it not sufficient to examine octanol-water partition coefficient (K_{ow}) as a predictor of uptake, as is done very widely? There are several shortcomings with this approach. These can be summarised:

- K_{ow} does not give detailed insight into intermolecular forces, and in particular the polar forces. This shortcoming can be illustrated in several ways, but one example is that two substances can have the same K_{ow} value but completely different affinities for water (or octanol) i.e. K_{ow} is a dimensionless relative property.

Although HSP does not address all these points, there are sufficient reasons to investigate alternatives to K_{ow} as a potentially-useful descriptor.

Access to HSP

HSP values were obtained from the HSPiP version 5.3.02 (https://www.hansen-solubility.com/HSPiP/).

Typical values of the HSP values[9] of organic molecules are:

δD: 11 to 23; the lowest numbers are typically for low molecular weight and /or certain atoms;
δP: 0 to 30, with 0 representing molecules of very high symmetry and no π bonds;
δH: 0 to 35, with 0 representing molecules containing no functionalities.

It should be noted that these values represent absolute energies.

Data for phosphate and phosphonate esters now follow. Graphical representation of the HSP data is given in the main body of the report.

The HSP values of the OPFRs cover a wide range of Hansen space.

Table 7 shows the basic molecular descriptors.

[9] For simplicity the HSP are given without their dimensions; they are absolute thermodynamic and not relative properties, and they all possess the unit $(Joules/cm^3)^{½}$.

Descriptors for phosphate esters

Table 9: Phosphate ester descriptors

Name		CAS number	EC number	MW g/mol	Mol Formula	P atoms	Alkyl	Aryl	Chloroalkyl	δD	δP	δH
Diphenyl (2-ethylhexyl) phosphate	EHDP	1241-94-7	214-987-2	362.4	C20H27O4P	1	1	2		18.3	6.2	5.4
Alkyl diphenyl phosphate		27460-02-2	431-760-5	418.5	C24H35O4P	1	1	2		18	5.7	4.8
Isodecyl diphenyl phosphate	IDDP	29761-21-5	249-828-6	390.4	C22H31O4P	1	1	2		18.1	6	4.8
Triethyl phosphate	TEP	78-40-0	201-114-5	182.15	C6H15O4P	1	3			15.9	10	7.2
Tris-(2-ethylhexyl) phosphate	TEHP	78-42-2	201-116-6	434.6	C24H51O4P	1	3			16.1	4.7	3.6
Tris(butoxyethyl) phosphate	TBEP	78-51-3	201-122-9	398.5	C18H39O7P	1	3			16	8.4	5.7
Tri-n-butyl phosphate	TBP	126-73-8	204-800-2	266.3	C12H27O4P	1	3			16.1	7.2	5.2
Triphenyl phosphate	TPP	115-86-6	204-112-2	326.3	C18H15O4P	1		3		20.4	7.2	6
Tris(methylphenyl) phosphate	TCP	1330-78-5	809-930-9	368.4	C21H21O4P	1		3		19.3	7.7	5.9
Trixylyl phosphate	TXP	25155-23-1	246-677-8	410.4	C24H27O4P	1		3		19	6.1	5.4
Cresyl diphenyl phosphate	CDP	26444-49-5	247-693-8	340.3	C19H17O4P	1		3		20	9.1	5.6
Isopropylated triphenyl phosphate	IPP	68937-41-7	273-066-3	382.4	C22H23O4P	1		3		19.1	7.7	4.5
Butylated triphenyl phosphate		220352-35-2	606-905-2	305.28	C16H18O4P	1		3		19.1	7.7	4.5
tris(2-chloroethyl) phosphate	TCEP	115-96-8	204-118-5	285.5	C6H12Cl3O4P	1			3	18	14.7	8.6
tris(2-chloro-1-methylethyl) phosphate	TCPP	13674-84-5	237-158-7	327.6	C9H18Cl3O4P	1			3	18	12	6.8
tris[2-chloro-1-(chloromethyl)ethyl] phosphate	TDCP	13674-87-8	237-159-2	430.9	C9H15Cl6O4P	1			3	19	15.9	7.1
Resorcinol bis (diphenyl phosphate)	RDP	57583-54-7	260-830-6	574.5	C30H24O8P2	2		5		22.9	7.2	5.9
Phosphoric trichloride, reaction products with 4,4'-isopropylidenediphenol and phenol	BDP	181028-79-5, 5945-33-5	425-220-8	692.6	C39H34O8P2	2		6		22.9	7.7	4.9

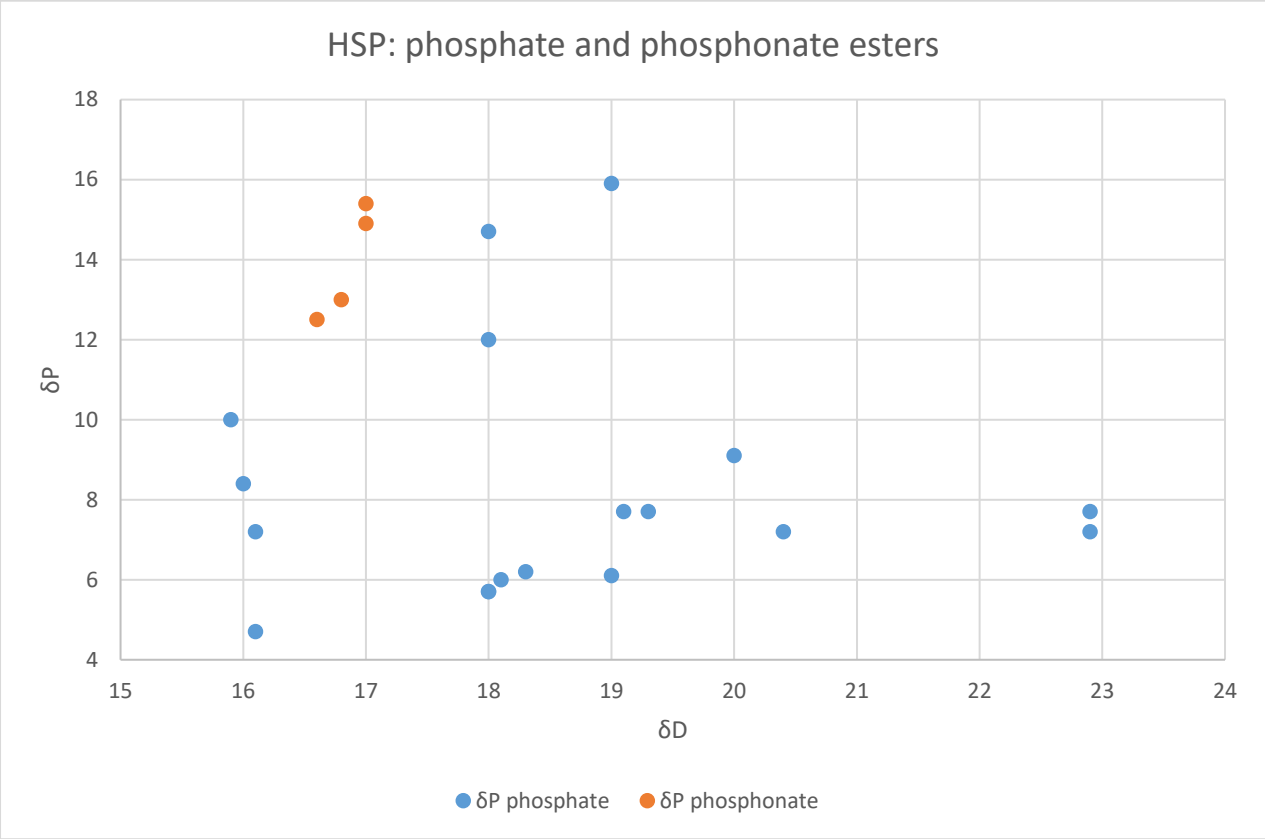
Descriptors for phosphonate esters

Table 10: Phosphonate ester descriptors

Name		CAS number	EC number	MW g/mol	Mol Formula	Alkyl	Ester	δD	δP	δH
DEEP - Diethyl ethyl phosphonate	DEEP	78-38-6	201-111-9	166.2	C6H15O3P	Ethyl	Ethyl	16.6	12.5	7.1
DMMP - Dimethyl methyl phosphonate	DMMP	756-79-6	756-79-6	124.1	C3H9O3P	Methyl	Methyl	17.0	15.4	9.5
Diethyl bis(hydroxyethyl) aminomethylphosphonate		2781-11-5	220-482-8	255.3	C9H22NO5P	bis hydroxy ethyl amino	Ethyl	17.0	14.9	14.8
DMPP - Dimethyl propane phosphonate	DMPP	18755-43-6	242-555-3	152.1	C5H13O3P	Propyl	Methyl	16.8	13.0	7.8

The phosphonate esters are now compared to the phosphonate esters in respect of HSP.

Figure 3: Comparison of the grouping of phosphate esters and phosphonate esters from HSP values



It can be seen that the two broad structural types are separated in HSP space.

11. Annex 2: REACH-relevant data tables

Data are all held in spreadsheets. Information presented here are extracts for the purpose of this report.

Phosphate esters

The items listed in Table 11 below are defined as follows[10]:

KOWWIN		Predicted log octanol-water partition coefficient
VP pred	Pa	Predicted vapour pressure
WS pred NT	mg/L	Predicted water solubility by the WATERNT program.
HENRYWIN bond	Pa m3/mol	Predicted Henry's Law constant (air-water partition) by the BOND method
log Koa		Predicted octanol-air partition coefficient
Koc MCI	L/kg	Predicted soil-water partition by the MCI method.

[10] Predicted physicochemical properties from EPIWEB are used because they give a self-consistent set; the ECHA web site dossier data is variable in presentation and quality.

Table 11: Phosphate ester physicochemical properties

Name		MW g/mol	KOWWIN	VP Pa pred	WS pred NT mg/L	HENRYWIN bond Pa m3/mol	log Koa	Koc MCI
Diphenyl (2-ethylhexyl) phosphate	EHDP	362.4	6.3	4.50E-03	1.80E-01	2.50E-02	8.4	3.20E+04
Alkyl diphenyl phosphate		418.5	8.34	2.70E-06	9.00E-04	7.80E-02	12.8	3.85E+05
Isodecyl diphenyl phosphate	IDDP	390.4	7.28	6.30E-06	1.70E-02	4.40E-02	10.2	5.10E+03
Triethyl phosphate	TEP	182.15	0.87	2.20E+01	1.20E+05	5.90E-02	6.63	6.40E+01
Tris-(2-ethylhexyl) phosphate	TEHP	434.6	9.5	8.10E-05	2.80E-04	9.70E+00	15	2.50E+06
Tris(butoxyethyl) phosphate	TBEP	398.5	3	1.65E-04	6.04E+02	1.20E-06	13.1	1.27E+03
Tri-n-butyl phosphate	TBP	266.3	3.82	4.70E-01	1.01E+02	3.20E-01	8.2	2.35E+03
Triphenyl phosphate	TPP	326.3	4.7	6.30E-05	4.70E+00	4.00E-03	8.5	1.10E+04
Tris(methylphenyl) phosphate	TCP	368.4	6.3	1.60E+00	1.40E-01	5.40E-03	9.6	4.70E+04
Trixylyl phosphate	TXP	410.4	7.98	2.70E-06	4.00E-03	7.30E-03	13.5	1.90E+05
Cresyl diphenyl phosphate	CDP	340.3	5.25	1.40E-05	1.50E+00	4.50E-03	10.3	1.80E+04
Isopropylated triphenyl phosphate	IPP	382.4	9.1	2.70E-06	5.00E-04	3.00E-02	14	1.20E+06
Butylated triphenyl phosphate		305.28	6.61	3.50E-06	1.00E-01	1.00E-02	12	7.50E+04
tris(2-chloroethyl) phosphate	TCEP	285.5	1.63	5.00E-02	5.60E+03	2.60E-03	5.3	3.88E+02
tris(2-chloro-1-methylethyl) phosphate	TCPP	327.6	2.89	8.00E-03	7.40E+02	6.00E-03	8.2	1.60E+03
tris[2-chloro-1-(chloromethyl)ethyl] phosphate	TDCP	430.9	3.65	3.80E-05	3.00E+01	2.60E-04	10.6	1.10E+04
Resorcinol bis (diphenyl phosphate)	RDP	574.5	7.4	2.70E-06	7.00E-03	3.00E-08	18.3	2.00E+08
Phosphoric trichloride, reaction products with 4,4'-isopropylidenediphenol and phenol	BDP	692.6	10	2.70E-06	2.00E-06	5.00E-09	21.7	1.00E+10

The properties follow the trends that would be expected based on structure.

Relevant environmental properties are now tabulated. Aquatic ecotoxicology is in Table 12b.

Table 12a: Phosphate ester environmental properties

Name		CAS number	EC Number	KOWWIN	VP Pa pred	WS pred NT mg/L	HENRYWIN bond Pa m3/mol	Koc MCI	Hydrolysis 20-25C	Degradation
Diphenyl (2-ethylhexyl) phosphate	EHDP	1241-94-7	214-987-2	6.3	4.50E-03	1.80E-01	2.50E-02	3.20E+04	No hydrolysis found	Readily biodegradable
Alkyl diphenyl phosphate		27460-02-2	431-760-5	8.34	2.70E-06	9.00E-04	7.80E-02	3.85E+05		
Isodecyl diphenyl phosphate	IDDP	29761-21-5	249-828-6	7.28	6.30E-06	1.70E-02	4.40E-02	5.10E+03		Readily biodegradable
Triethyl phosphate	TEP	78-40-0	201-114-5	0.87	2.20E+01	1.20E+05	5.90E-02	6.40E+01	No hydrolysis found	Not biodegradable
Tris-(2-ethylhexyl) phosphate	TEHP	78-42-2	201-116-6	9.5	8.10E-05	2.80E-04	9.70E+00	2.50E+06	No hydrolysis found	Not biodegradable
Tris(butoxyethyl) phosphate	TBEP	78-51-3	201-122-9	3	1.65E-04	6.04E+02	1.20E-06	1.27E+03	No data	Readily biodegradable
Tri-n-butyl phosphate	TBP	126-73-8	204-800-2	3.82	4.70E-01	1.01E+02	3.20E-01	2.35E+03	No data	Readily biodegradable
Triphenyl phosphate	TPP	115-86-6	204-112-2	4.7	6.30E-05	4.70E+00	4.00E-03	1.10E+04	3 d at pH 9	Readily biodegradable
Tris(methylphenyl) phosphate	TCP	1330-78-5	809-930-9	6.3	1.60E+00	1.40E-01	5.40E-03	4.70E+04	6.6 d at pH 9	Readily biodegradable
Trixylyl phosphate	TXP	25155-23-1	246-677-8	7.98	2.70E-06	4.00E-03	7.30E-03	1.90E+05	No hydrolysis found	Not biodegradable

Name		CAS number	EC Number	KOWWIN	VP Pa pred	WS pred NT mg/L	HENRYWIN bond Pa m3/mol	Koc MCI	Hydrolysis 20-25C	Degradation
Cresyl diphenyl phosphate	CDP	26444-49-5	247-693-8	5.25	1.40E-05	1.50E+00	4.50E-03	1.80E+04	No data	Readily biodegradable
Isopropylated triphenyl phosphate	IPP	68937-41-7	273-066-3	9.1	2.70E-06	5.00E-04	3.00E-02	1.20E+06	6 d at pH 9	Not biodegradable
Butylated triphenyl phosphate		220352-35-2	606-905-2	6.61	3.50E-06	1.00E-01	1.00E-02	7.50E+04	No study	Readily biodegradable
tris(2-chloroethyl) phosphate	TCEP	115-96-8	204-118-5	1.63	5.00E-02	5.60E+03	2.60E-03	3.88E+02	Does not hydrolyse	
tris(2-chloro-1-methylethyl) phosphate	TCPP	13674-84-5	237-158-7	2.89	8.00E-03	7.40E+02	6.00E-03	1.60E+03	Does not hydrolyse	Possible inherently biodegradable
tris[2-chloro-1-(chloromethyl)ethyl] phosphate	TDCP	13674-87-8	237-159-2	3.65	3.80E-05	3.00E+01	2.60E-04	1.10E+04	pH 9 120 d	Not biodegradable
Resorcinol bis (diphenyl phosphate)	RDP	57583-54-7	260-830-6	7.4	2.70E-06	7.00E-03	3.00E-08	2.00E+08	pH 4 11 d; pH 9 21 d	
Phosphoric trichloride, reaction products with 4,4'-isopropylidenediphenol and phenol	BDP	181028-79-5, 5945-33-5	425-220-8	10	2.70E-06	2.00E-06	5.00E-09	1.00E+10		Not biodegradable

Table 12b: Phosphate ester aquatic ecotoxicology

The predicted values from ECOSAR are indicative only and for simplicity only the value for invertebrates is tabulated.

Name		CAS number	EC Number	ECOSAR esters chronic NOEC invert µg/L	Aquatic chronic - fish	Aquatic chronic - inverts	Aquatic chronic – algal growth
Diphenyl (2-ethylhexyl) phosphate	EHDP	1241-94-7	214-987-2	39	71d NOE+AI2:AI16C 21 ug/L	21d NOEC ca. 18 µg/L	72h NOEC 72 ug/L
Alkyl diphenyl phosphate		27460-02-2	431-760-5	1.3			
Isodecyl diphenyl phosphate	IDDP	29761-21-5	249-828-6	6	90d NOEC 57 ug/L	21d NOEC ca. 5 µg/L	Result not clear
Triethyl phosphate	TEP	78-40-0	201-114-5	2.40E+05	No data	21d NOEC 32 mg/L	72h EC10 127 mg/L
Tris-(2-ethylhexyl) phosphate	TEHP	78-42-2	201-116-6	1.80E-01	No data	21 d NOEC 1 mg/L (doubtful!)	No effects at limit of solubility
Tris(butoxyethyl) phosphate	TBEP	78-51-3	201-122-9	1.30E+04	No data	Acute EC50 51 mg/L	72h 7.6 mg/L
Tri-n-butyl phosphate	TBP	126-73-8	204-800-2	2140	50d NOEC 8.3 mg/L	21d NOEC 1.3 mg/L	72h EC10 0.37 mg/L
Triphenyl phosphate	TPP	115-86-6	204-112-2	570	NOEC 3 ug/L duration not stated in CSR	21d NOEC 250 µg/L	72h EC10 0.25 mg/L
Tris(methylphenyl) phosphate	TCP	1330-78-5	809-930-9	37		21d NOEC 100 µg/L	
Trixylyl phosphate	TXP	25155-23-1	246-677-8	2	No effects at solubility limit	21d NOEC ca. 6 - 100 µg/L	No effects at solubility limit
Cresyl diphenyl phosphate	CDP	26444-49-5	247-693-8	228	No data	21d NOEC 120 µg/L	72h NOEC 200 ug/L

Name		CAS number	EC Number	ECOSAR esters chronic NOEC invert µg/L	Aquatic chronic - fish	Aquatic chronic - inverts	Aquatic chronic – algal growth
Isopropylated triphenyl phosphate	IPP	68937-41-7	273-066-3	0.4	33d NOEC 3.1 ug/L	21d NOEC 42 µg/L	72h NOEC 310 ug/L
Butylated triphenyl phosphate		220352-35-2	606-905-2	24	90d NOEC 93 ug/L	21d NOEC ca. 36 µg/L	72h NOEC 50 ug/L
tris(2-chloroethyl) phosphate	TCEP	115-96-8	204-118-5	1.00E+05	No data		72h NOEC 100 mg/L
tris(2-chloro-1-methylethyl) phosphate	TCPP	13674-84-5	237-158-7	1.30E+04	No data	21d NOEC 32 mg/L	72h NOEC 13 mg/L
tris[2-chloro-1-(chloromethyl)ethyl] phosphate	TDCP	13674-87-8	237-159-2	4660	180d NOEC 2 ug/L	NOEC 1 mg/L	72 h NOEC 1.2 mg/L
Resorcinol bis (diphenyl phosphate)	RDP	57583-54-7	260-830-6	9	No data		
Phosphoric trichloride, reaction products with 4,4'-isopropylidenediphenol and phenol	BDP	181028-79-5, 5945-33-5	425-220-8	0.1	No effects at limit of solubility Fish NOEC: 5mg/L	Daphnia repro: NOEC >100 mg/L Chironomus long-term: >=1000 mg/kg sed Lumbriculus long-term: NOEC >=1000 mg/kg sed	No effects at limit of solubility 72h NOEC >1 mg/L

Table 13a gives the results from in vivo mammalian studies. Table 13b summarises results from *in vitro* genotoxicology.

Table 13a: Phosphate ester health information

Since this is not an in-depth review, species tested are not stated. For some information sources the exact OECD number or equivalent could not be established.

Name	CAS number	EC number	Repeat dose oral mammalian (rodent)	Carcinogenicity	Fertility	Developmental	Neurotoxicity	Endocrine
Diphenyl (2-ethylhexyl) phosphate	1241-94-7	214-987-2	CSR 90 d LOAEL 7.3 mg/kg/d; liver effects	No data	Study available OECD 415	Study available OECD 415	Studies available OECD 418	No data
Alkyl diphenyl phosphate	27460-02-2	431-760-5	Pubchem reports 90 d study					
Isodecyl diphenyl phosphate	29761-21-5	249-828-6	CSR: LOAEL 10 mg/kg/d OECD 408; a variety of effects.	No data	No study	Study available OECD 414	Studies available OECD 418	No data
Triethyl phosphate	78-40-0	201-114-5	CSR: NOAEL oral 200 mg/kg/d; liver size. 90 d OECD 408	No data	No study	Study available OECD 414	Study available	Study available
Tris-(2-ethylhexyl) phosphate	78-42-2	201-116-6	CSR: NOAEL 1000 mg/kg/d in 90 d study (body weight)	Studies available	Study available OECD 443	Study available OECD 414	Study available	No data
Tris(butoxyethyl) phosphate	78-51-3	201-122-9	CSR: NOAEL oral 1000 mg/kg/d, 28 d OECD 407; no significant effects.	No data	No study	Study available OECD 414	No data	No data
Tri-n-butyl phosphate	126-73-8	204-800-2	CSR: NOEL = 75 mg/kg/d (90 d study).	Classified	Study available	Study available.	Study available	No data
Triphenyl phosphate	115-86-6	204-112-2	CSR: NOAEL oral 105 mg/kg/d OECD 408; liver weigh increase.		OECD 415 available	Study available	Study available	Study available
Tris(methylphenyl) phosphate	1330-78-5	809-930-9	LOAEL 50 mg/kg/d	No effects	Classified	Data available	Effects associated with ortho isomer	Study available
Trixylyl phosphate	25155-23-1	246-677-8	NOAEL oral 30 mg/kg/d	No data	Classified	Data available	No effects	No data

Name	CAS number	EC number	Repeat dose oral mammalian (rodent)	Carcinogenicity	Fertility	Developmental	Neurotoxicity	Endocrine
Cresyl diphenyl phosphate	26444-49-5	247-693-8	CSR: NOAEL oral 63 mg/kg/d OECD 407 28 d; liver and related effects	No data	OECD 422 available	OECD 422 available	No data	
Isopropylated triphenyl phosphate	68937-41-7	273-066-3	CSR: NOAEL oral 25 mg/kg/d	No data	Classified	Data available; further tests proposed.	No effects	No data
Butylated triphenyl phosphate	220352-35-2	606-905-2	CSR: 90 d NOAEL oral 108 mg/kg/d, OECD 408	No data	Screening study OECD 421 on both high and low TPP substances	OECD 414 on both high and low TPP substances	OECD 418 on high and low TPP substances	No data
Tris(2-chloroethyl) phosphate	115-96-8	204-118-5	NOAEL 350 mg/kg/d 14 d study.	Classified	Classified	Study available	Studies available	No data
Tris(2-chloro-1-methylethyl) phosphate	13674-84-5	237-158-7	CSR: LOAEL 52 mg/kg/d 90 d	Report awaited, may be carcinogenic (weakly)	Study available OECD 416	Study available OECD 414	Studies available	In vitro study available
Tris[2-chloro-1-(chloromethyl)ethyl] phosphate	13674-87-8	237-159-2	CSR: LOAEL 5 mg/kg/d; 2 y study Target organs: urogenital: kidneys; digestive: liver; glandular: thyroid	Classified	Information from carcinogenicity study	Studies available	No data	No data
Resorcinol bis (diphenyl phosphate)	57583-54-7	260-830-6	CSR: NOAEL oral 1000 mg/kg/d, 90 d OECD 408	No data	Study available OECD 416	Study available OECD 414	Studies available	
Phosphoric trichloride, reaction products with 4,4'-isopropylidenediphenol and phenol	181028-79-5, 5945-33-5	425-220-8	CSR: NOAEL oral 1000 mg/kg/d, 90 d OECD 408; no significant effects.	No data	Screening study OECD 421	Screening study OECD 421	No data	

Table 13b: Phosphate ester health information (genotoxicology)

Name	CAS number	EC number	Mutagenicity in vitro	Mutagenicity in vivo
Diphenyl (2-ethylhexyl) phosphate	1241-94-7	214-987-2	All studies negative	Negative
Alkyl diphenyl phosphate	27460-02-2	431-760-5		
Isodecyl diphenyl phosphate	29761-21-5	249-828-6	All studies negative	
Triethyl phosphate	78-40-0	201-114-5	All studies negative	Negative
Tris-(2-ethylhexyl) phosphate	78-42-2	201-116-6	All studies negative	Negative
Tris(butoxyethyl) phosphate	78-51-3	201-122-9	All studies negative	Negative
Tri-n-butyl phosphate	126-73-8	204-800-2	All studies negative	Negative
Triphenyl phosphate	115-86-6	204-112-2	All studies negative	
Tris(methylphenyl) phosphate	1330-78-5	809-930-9		
Trixylyl phosphate	25155-23-1	246-677-8	All studies negative	
Cresyl diphenyl phosphate	26444-49-5	247-693-8	One positive study	Negative
Isopropylated triphenyl phosphate	68937-41-7	273-066-3	All studies negative	Negative

Name	CAS number	EC number	Mutagenicity in vitro	Mutagenicity in vivo
Butylated triphenyl phosphate	220352-35-2	606-905-2	All studies negative	Not required
Tris(2-chloroethyl) phosphate	115-96-8	204-118-5	All studies negative	Negative
Tris(2-chloro-1-methylethyl) phosphate	13674-84-5	237-158-7	Some positive results	Negative
Tris[2-chloro-1-(chloromethyl)ethyl] phosphate	13674-87-8	237-159-2	Some positive results	Negative
Resorcinol bis (diphenyl phosphate)	57583-54-7	260-830-6	All studies negative	Negative
Phosphoric trichloride, reaction products with 4,4'-isopropylidenediphenol and phenol	181028-79-5, 5945-33-5	425-220-8	All studies negative	Not required

Table 14: Phosphate ester classifications

Name	CAS number	EC number	pinfa classification	ECHA or others
Diphenyl (2-ethylhexyl) phosphate	1241-94-7	214-987-2	?	No data
Alkyl diphenyl phosphate	27460-02-2	431-760-5	?	H315 H412 PubChem from EU
Isodecyl diphenyl phosphate	29761-21-5	249-828-6	Not classified	H413
Triethyl phosphate	78-40-0	201-114-5	H302, H319	H302, H319
Tris-(2-ethylhexyl) phosphate	78-42-2	201-116-6	Not classified	H315, H319
Tris(butoxyethyl) phosphate	78-51-3	201-122-9	Not classified	H315 pubchem
Tri-n-butyl phosphate	126-73-8	204-800-2	H351, H302, H315, H412	H302, H315, H351
Triphenyl phosphate	115-86-6	204-112-2	H400, H411	H400, H410
Tris(methylphenyl) phosphate	1330-78-5	809-930-9	H360, H400, H410	H400, H410, H361
Trixylyl phosphate	25155-23-1	246-677-8	H360, H373, H400, H410	H400, H410, H360F,H373, H319, H411
Cresyl diphenyl phosphate	26444-49-5	247-693-8	H400, H412	No data

Name	CAS number	EC number	pinfa classification	ECHA or others
Isopropylated triphenyl phosphate	68937-41-7	273-066-3	H361, H373, H410	H361, H373, H410
Butylated triphenyl phosphate	220352-35-2	606-905-2	H400, H410	H400, H410, H411
tris(2-chloroethyl) phosphate	115-96-8	204-118-5		H411, H351, H360F, H302
tris(2-chloro-1-methylethyl) phosphate	13674-84-5	237-158-7	H302	H302
tris[2-chloro-1-(chloromethyl)ethyl] phosphate	13674-87-8	237-159-2		H351, H410
Resorcinol bis (diphenyl phosphate)	57583-54-7	260-830-6	Not classified	H411 pubchem
Phosphoric trichloride, reaction products with 4,4'-isopropylidenediphenol and phenol	181028-79-5, 5945-33-5	425-220-8	Not classified	Not classified
Mixtures of esters of phophoric acid	1003300-73-9			H412, H315
Oligomeric ethyl ethylene phosphate	184538-58-7	606-033-2		Not classfied

Phosphonate esters

Table 15: Phosphonate ester physicochemical properties

Name	CAS number	Log Kow predicted KOWWIN	VP Pa predicted	WS mg/L predicted NT method	HENRYWIN bond Pa m3/mol	log Koa	Koc MCI
DEEP - Diethyl ethyl phosphonate	78-38-6	0.89	5.30E+01	2.50E+05	0.3	4.6	3.50E+01
DMMP - Dimethyl methyl phosphonate	756-79-6	-0.59	1.23E+02	1.00E+06	1.30E-01	3.68	5.4
Diethyl bis(hydroxyethyl) aminomethylphosphonate	2781-11-5	-1.94	1.20E-05	1.00E+06	2.60E-10	12.2	10
DMPP - Dimethyl propane phosphonate	18755-43-6	0.4	6.50E+01	8.00E+05	2.20E-01	4.45	1.93E+01

Table 16: Phosphonate ester environmental data

Name		CAS number	EC number	ECOSAR esters chronic NOEC invert µg/L	Hydrolysis 20-25C	Degradation	Aquatic - inverts
DEEP - Diethyl ethyl phosphonate	DEEP	78-38-6	201-111-9	2.18E+05		Not readily biodegradable	
DMMP - Dimethyl methyl phosphonate	DMMP	756-79-6	756-79-6	2.10E+06			
Diethyl bis(hydroxyethyl) aminomethylphosphonate		2781-11-5	220-482-8	7.50E+04	CSR: 1pH 4 179 d; pH 7 26 d; pH 9 14 h	Not readily biodegradable	
DMPP - Dimethyl propane phosphonate	DMPP	18755-43-6	242-555-3	4.70E+05	CSR: no hydrolysis	Not readily biodegradable	No short term effects

Table 17: Phosphonate ester health data

Name		CAS number	EC number	Repeat dose oral mammalian	Carcinogenicity	Fertility	Developmental	Neurotoxicity
DEEP - Diethyl ethyl phosphonate	DEEP	78-38-6	201-111-9	NOAEL 150 mg/kg/d				
DMMP - Dimethyl methyl phosphonate	DMMP	756-79-6	756-79-6	NOAEL 1000 mg/kg/d		Classified		
Diethyl bis(hydroxyethyl) aminomethylphosphonate		2781-11-5	220-482-8	CSR: NOAEL 500 mg/kg/d 90 d OECD 408	(positive in vitro genotox)	Screening study OECD 421		Study available (K 4)
DMPP - Dimethyl propane phosphonate	DMPP	18755-43-6	242-555-3	CSR: NOAEL 20 mg/kg/d; OECD 407 28 d	No study	Classified	No study	No study

Table 18: Phosphonate ester classifications

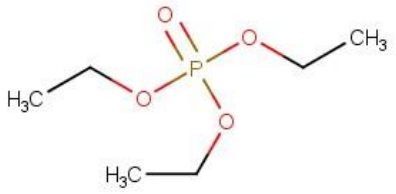
Name		CAS number	EC number	ECHA
DEEP - Diethyl ethyl phosphonate	DEEP	78-38-6	201-111-9	H411, H302
DMMP - Dimethyl methyl phosphonate	DMMP	756-79-6	756-79-6	H319, H340, H361
Diethyl bis(hydroxyethyl) aminomethylphosphonate		2781-11-5	220-482-8	Not classified
DMPP - Dimethyl propane phosphonate	DMPP	18755-43-6	242-555-3	H360, H319?

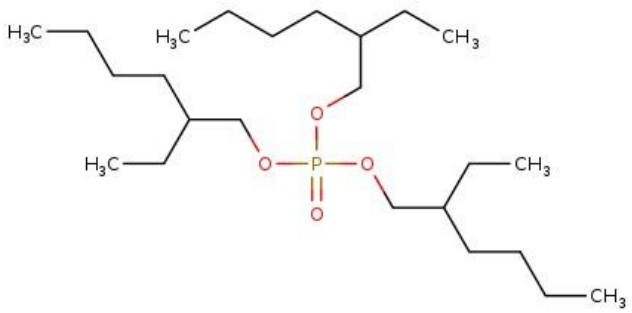
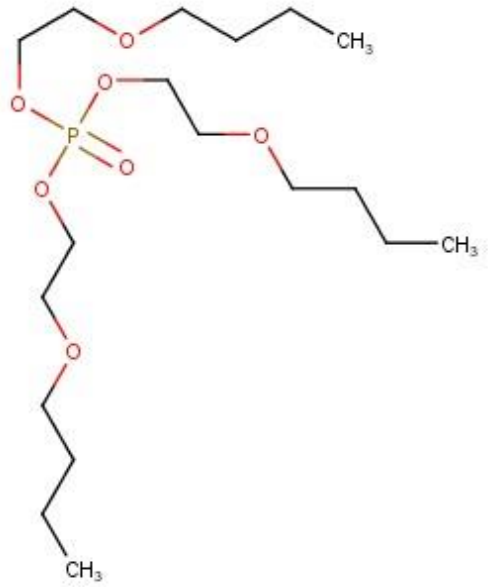
12. Annex 3: Graphics of structures

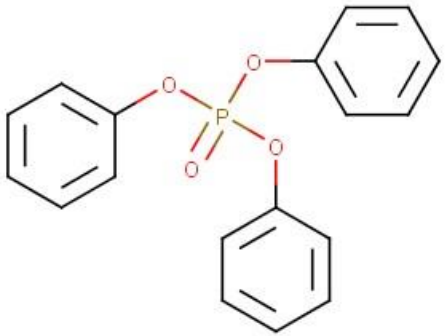
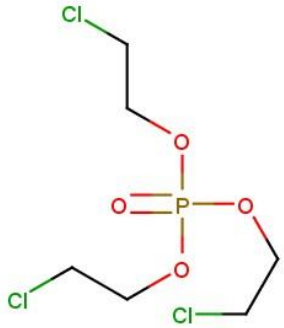
These tables show the structures graphically.

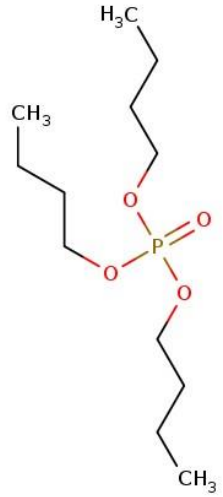
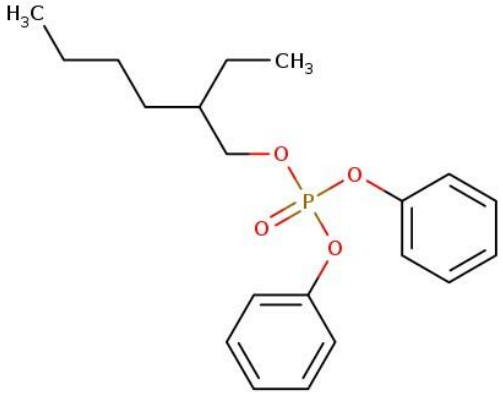
Phosphate esters

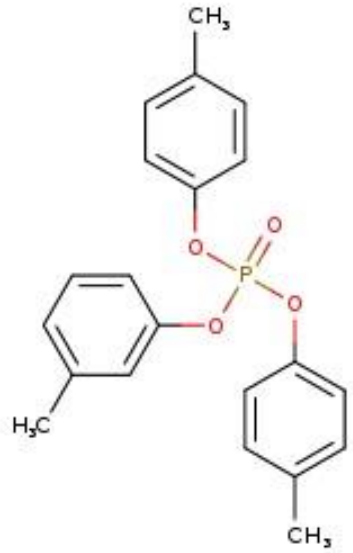
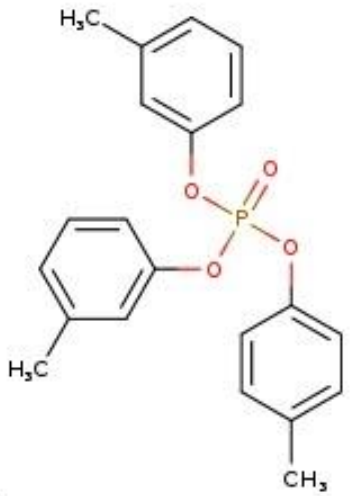
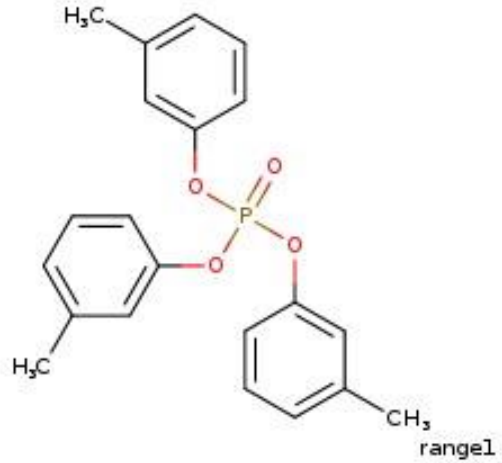
Table 19: Phosphate esters

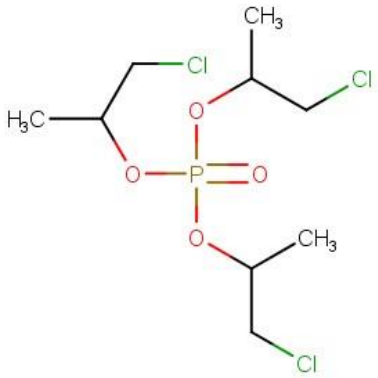
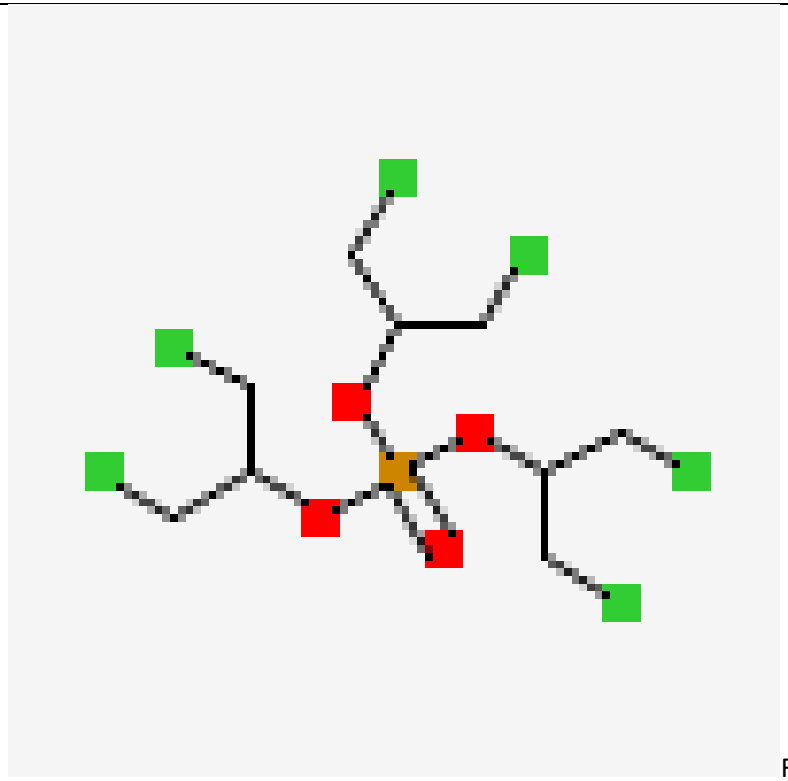
Name	Known as	CAS number	EC number	Structure as shown on ECHA website (unless from PubChem)
Triethyl phosphate	TEP	78-40-0	201-114-5	

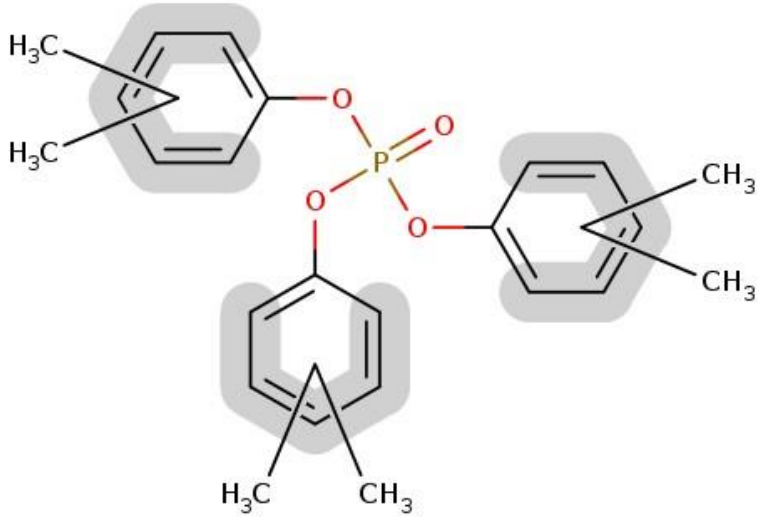
Tris-(2-ethylhexyl) phosphate	TEHP	78-42-2	201-116-6	
Tris(butoxyethyl) phosphate	TBEP	78-51-3	201-122-9	

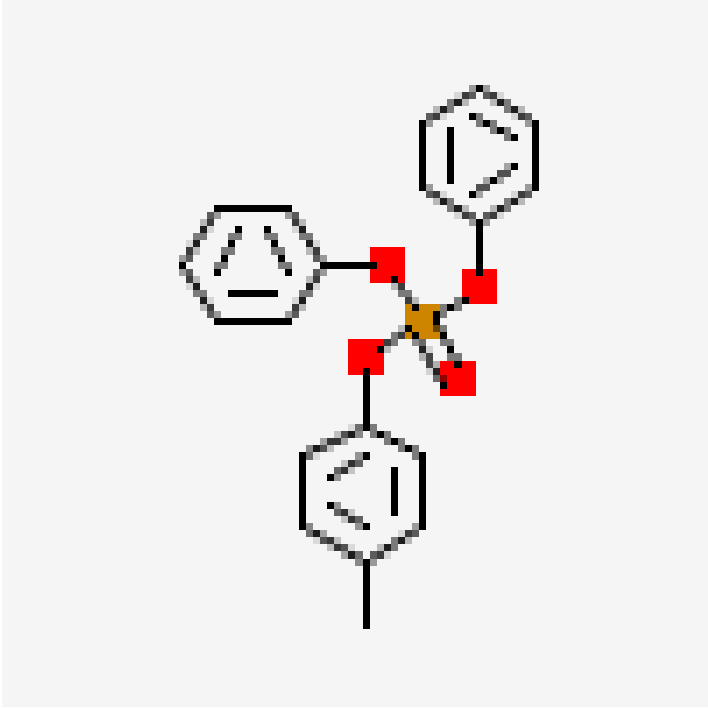
triphenyl phosphate	TPP	115-86-6	204-112-2	
tris(2-chloroethyl) phosphate	TCEP	115-96-8	204-118-5	

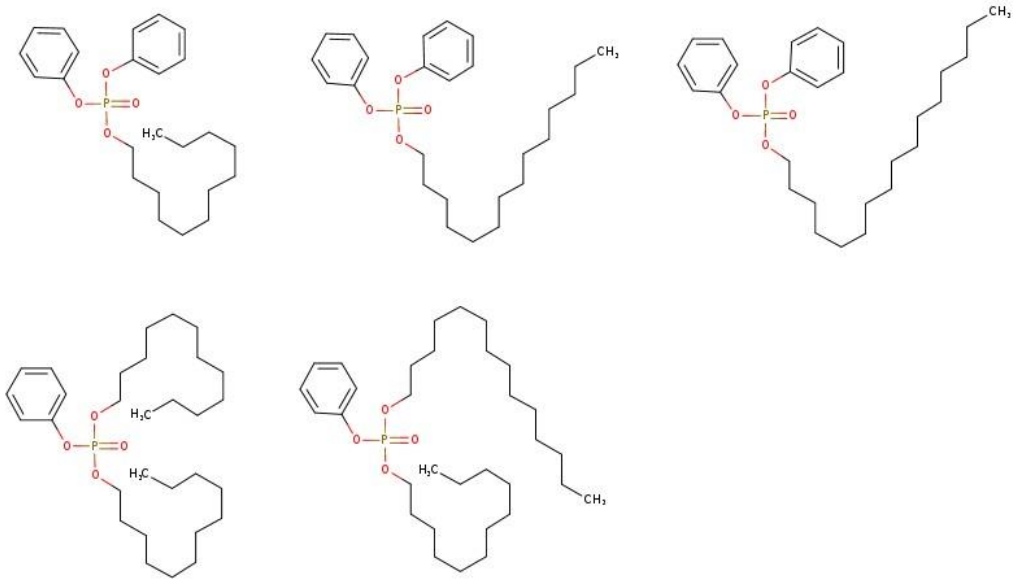
Tri n-butyl phosphate	TBP	126-73-8	204-800-2	
Diphenyl (2-ethylhexyl) phosphate	EHDP	1241-94-7	214-987-2	

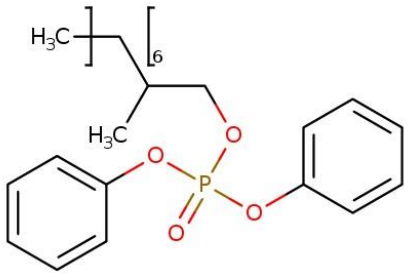
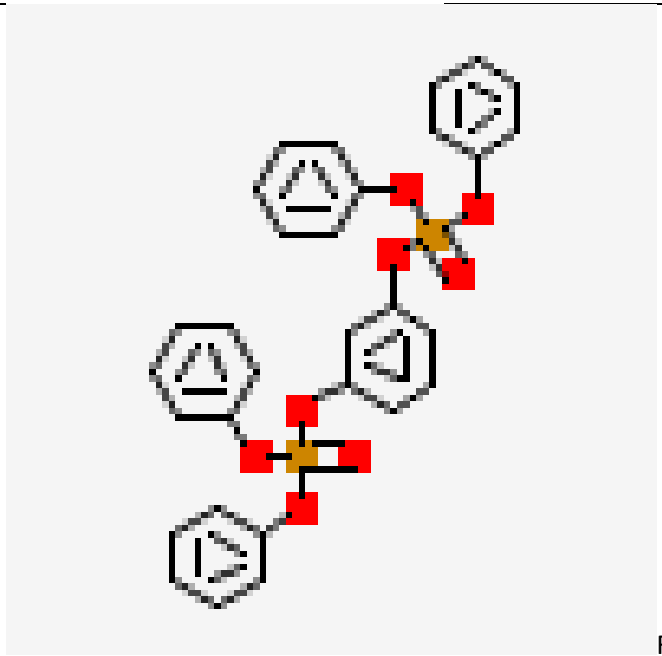
Tris(methylphenyl) phosphate*	TCP	1330-78-5	809-930-9	 rangel  rangel  rangel

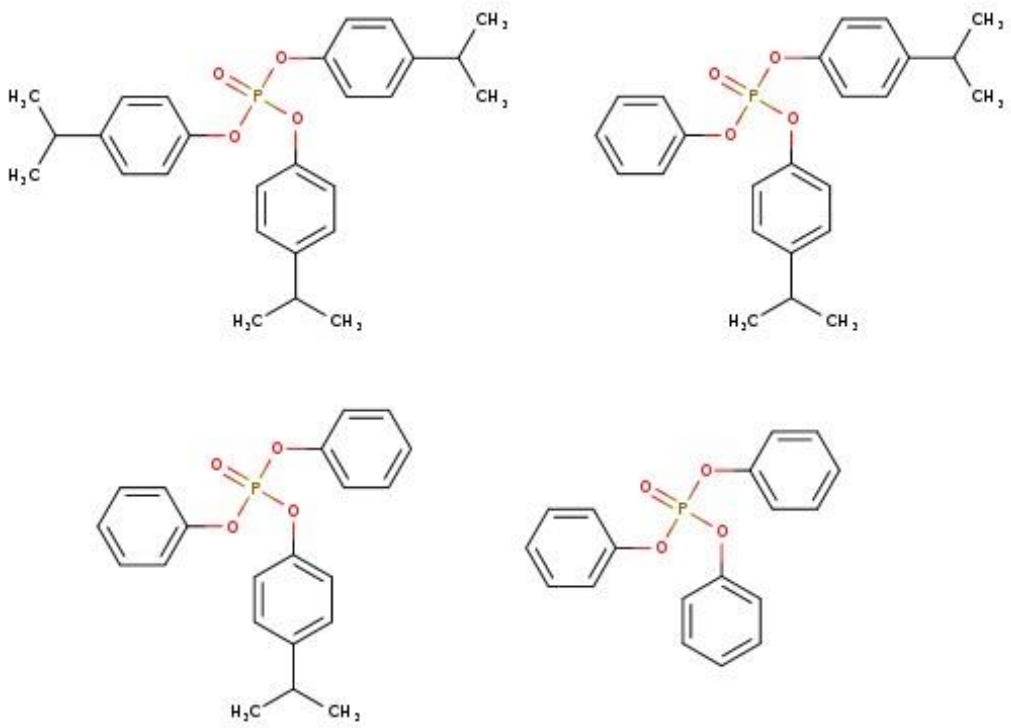
tris(2-chloro-1-methylethyl) phosphate*	TCPP	13674-84-5 1244733-77-4	237-158-7	
tris[2-chloro-1-(chloromethyl)ethyl] phosphate	TDCP	13674-87-8	237-159-2	 From PubChem

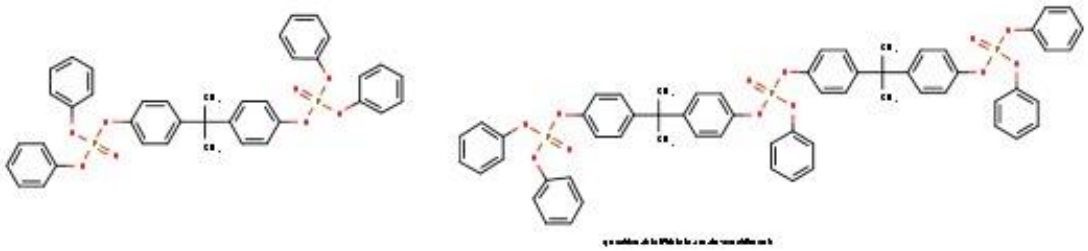
Trixylyl phosphate*	TXP	25155-23-1	246-677-8	

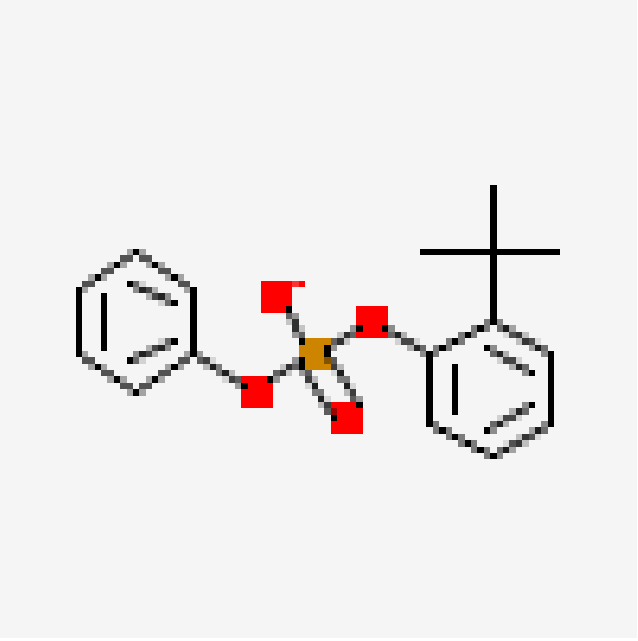
Cresyl diphenyl phosphate*	CDP	26444-49-5	247-693-8	 From PubChem

Alkyl diphenyl phosphate* (ECHA states this to be dodecyl)		27460-02-2	431-760-5	

Isodecyl diphenyl phosphate	IDDP	29761-21-5	249-828-6	
Resorcinol bis (diphenyl phosphate)*	RDP	57583-54-7	260-830-6 701-337-2	 From PubChem

Isopropylated triphenyl phosphate*	IPP	68937-41-7	273-066-3	

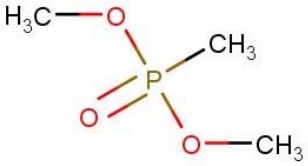
Phosphoric trichloride, reaction products with 4,4'-isopropylidenediphenol and phenol	BDP	181028-79-5, 5945-33-5	425-220-8	

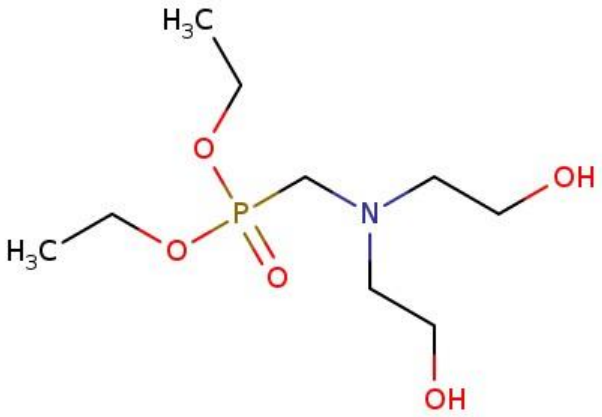
Butylated triphenyl phosphate		220352-35-2	700-990-0 939-505-4	 FROM PUBCHEM
Oligomeric ethyl ethylene phosphate**		184538-58-7	606-033-2	
Mixtures of esters of phosphoric acid**		1003300-73-9		

*multi-constituent; **UVCB; not discussed further herein

Other substances that are not part of this study but for which there is some literature data can include pure constituents of some of the above, where they are multi-constituent.

Table 18: Phosphonate esters

Name	Known as	CAS number	EC number	Structure as shown on ECHA website
Diethyl ethyl phosphonate	DEEP	78-38-6	201-111-9	
Dimethyl methyl phosphonate	DMMP	756-79-6	212-025-3	

Diethyl bis(hydroxyethyl) aminomethylphosphonate		2781-11-5	220-482-8	
Dimethyl propane phosphonate	DMPP	18755-43-6	242-555-3