SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

Triphenyl Phosphite (TPP)

EC No 202-908-4

CAS No 101-02-0

Evaluating Member State(s): UK

Dated: March 2019

Evaluating Member State Competent Authority

UK REACH CA
Health and Safety Executive
Redgrave Court
Merton Road
Bootle
Merseyside
L20 7HS
Email:ukreachca@hse.gov.uk

Chemicals Assessment Unit
Environment Agency
Red Kite House, Howbery Park
Wallingford
Oxfordshire, OX10 8BD
Email: UKREACHENV@environment-agency.gov.uk

Year of evaluation in CoRAP: 2013

Before concluding the substance evaluation a Decision to request further information was issued on: 2 December 2015

Further information on registered substances here:

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

DISCLAIMER

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

Foreword

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

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

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

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

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

Contents

Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

Triphenyl phosphite (TPP) was originally selected for substance evaluation in order to clarify concerns about:

- Human health: screening studies revealed adverse effects on reproductive, behavioural and neurotoxicity endpoints. The substance is a suspected reproductive toxicant and might possess endocrine disrupting properties (effects on adrenal glands, testes, kidney, brain).

- Human exposure: the substance is self-classified as a skin sensitiser and has wide dispersive use including consumer use and combined exposure. Exposure information and risk characterisation information is therefore missing; it is not possible to assess if the risks are being managed.

- Environment: the environmental fate properties of triphenyl phosphite (TPP) and related phenyl/alkyl phosphites generally include low water solubility, low vapour pressure, and rapid hydrolysis to phosphorous acid and corresponding alcohols (in the case of triphenyl phosphite it is phenol). As some phenols possess oestrogenic or endocrine-disruptor activities, there is a concern that the registered substance might be a potential ED (human health screening studies on TPP reported affected relative paired testes, adrenal glands, kidney and brain weights).

During the evaluation also other concerns were identified:

For human health, additional concerns related to repeated-dose toxicity and genotoxicity.

For the environment, additional concerns related primarily to a lack of clarity over the expected rapid hydrolysis and the ready biodegradation of TPP and nature of its hydrolysis products. There were concerns over the methodology and reporting from the available abiotic and biotic degradation studies, which were performed under non-standard conditions owing to the low solubility and apparent rapid hydrolysis of TPP.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

TPP is listed in Annex VI of the CLP regulation[2] (Index no.: 015-105-00-7, ATP CLP00).

TPP has been subject to three compliance checks; two have been concluded, one is still ongoing at the time of this report (March 2019).

3. CONCLUSION OF SUBSTANCE EVALUATION

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

Table 1

CONCLUSION OF SUBSTANCE EVALUATION

[2] Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures.

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

Human health

Initial concerns

The evaluation clarified the initial concern for reproductive toxicity (adverse effects on reproductive endpoints): no specific developmental or fertility effects were observed in the data available at the time of this evaluation. Further information was therefore not requested. The concern for neurotoxicity was clarified and no further information was requested.

The available evidence indicates that TPP is not an endocrine disruptor in relation to human health, because it did not produce clear effects on the endocrine system or endocrine-mediated functions. The concern was clarified and no further information was requested.

During the evaluation it was noted that the available data show that TPP meets the classification criteria for Skin Sens 1A (H317); however, this classification is not currently applied by the Registrant(s) nor the notifiers to the Classification and Labelling Inventory.

Additional concerns

Information from a 10-day range-finding study and the combined repeated-dose toxicity/reproductive toxicity screening study indicated that TPP meets the criteria for classification for repeated-dose toxicity (STOT RE 2). The eMSCA recommended that the registrants apply this classification, and in the latest update to the registration dossier it is noted that the classification STOT RE 2; H373 (nervous system) has been applied by the registrants. Further information was not requested regarding repeated dose toxicity.

The evaluation raised concern over the robustness of the available information on genotoxicity; an *in vitro* micronucleus test (test method: EU B.49, OECD 487) was requested. In response to the request, the registrants provided an *in vitro* mammalian cell micronucleus test in human peripheral blood lymphocytes (OECD 487). They also provided a bacterial reverse mutation test (OECD 471). Both studies were conducted on the registered substance, and both studies were negative. Therefore, the available genotoxicity package is now considered to be sufficiently robust, and there is no longer a concern for genotoxicity.

Exposure (related to human health)

As an outcome from this evaluation, several follow on actions have been identified for registrants to improve the quality of their registrations. These are listed in Part B, section 7.13 and include actions that should already have been taken in response to the decision issued on 2 December 2015. In particular, REACH Annex II clearly states that registrants must provide information on the types of gloves to be worn when handling the substance or mixture including the types of material and its thickness, also typical or minimum breakthrough times. If other parts of the body need protecting, the type and quality of this protection equipment shall also be specified.

Several registrants have still not provided any information on glove types, materials etc despite this information being asked for in the decision.

Environment

Initial concerns

As some phenolic substances are implicated as possessing oestrogenic or endocrine-disruptor (ED) activities, there was a concern that the registered substance might be a potential environmental as well as human health ED. An assessment of the ED potential of TPP based on information from the human health data set, as well as that on its major environmental degradant, phenol, indicates that TPP has a low ED potential.

Additional concerns

For the environment, additional concerns were raised relating to a lack of clarity over the proposed rapid hydrolysis and ready biodegradation of TPP and the precise nature of its hydrolysis products. There was uncertainty regarding the methodology and reporting from the initially available abiotic and biotic degradation studies, which were performed under non-standard conditions owing to the low solubility and apparent rapid hydrolysis of TPP.

The lead registrants submitted new reliable hydrolysis and ready biodegradation studies on TPP which confirm its rapid hydrolysis and biodegradation, predominantly to phenol - for which an EU Risk Assessment Report (2006) is available. The hazard and risk assessments for TPP are therefore based on phenol and no concerns relating to the proposed uses have been identified in CSRs.

4. FOLLOW-UP AT EU LEVEL

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

4.1.1. Harmonised Classification and Labelling

The eMSCA has concluded that TPP meets the criteria for classification with Skin Sens. 1A. It has also obtained high RCRs for dermal exposure in its risk characterisation. Both of these factors indicate there is a need to minimise potential skin exposure wherever this may occur. Based on the information currently presented in CSRs, it is not clear to the eMSCA that downstream users are being provided with sufficient information to manage the identified risk.

Registrants that were active in January 2019 classify as either Skin Sens 1 or Skin Sens 1B, but several notifications to the CLP inventory do not identify skin sensitisation as a relevant hazard[3]. This under-classification raises the concern that downstream users may take insufficient precautions to manage the skin sensitisation hazard putting worker's health at risk. It is also relevant to note that the use of Skin Sens 1 or Skin Sens 1B means that mixtures containing TPP only need to be classified for skin sensitisation if the mixture contains 1% or more TPP. Information provided in registrations suggests that polymer formulations and coating/adhesive mixtures containing < 1% TPP are supplied to the market. This raises a concern that such mixtures may not carry the correct classification based on the skin sensitising potential of TPP. If the Skin Sens 1A classification is applied, any formulation containing 0.1% or more TPP must be classified as a potential skin sensitiser.

[3] CLP inventory checked 1 March 2019

Turning to the RCRs calculated by the eMSCA, the highest dermal RCRs were obtained for the use of polymer formulations and coating/adhesive mixtures. CSRs do not identify gloves as being necessary for several contributing scenarios associated with these uses. This raises a further concern for the possibility for adverse systemic effects in addition to skin sensitisation and highlights the need for strong signals to be sent to downstream users about the need to minimise skin exposure even when using mixtures containing low concentrations of TPP.

If the harmonised classification is updated to include skin sensitisation (this hazard is currently not recognised in the harmonised classification) this will send a clear message about the need to minimise skin exposure.

The eMSCA has also concluded that TPP meets the criteria for classification with STOT RE 2. In the most recent update of the registration dossier, the registrants have included the STOT RE 2 classification, however the classification and labelling inventory shows that many notifiers still do not apply this notification.

The eMSCA also notes that the lead registrants do not consider that the current harmonised environmental classifications (Aquatic Acute 1 and Aquatic Chronic 1) are justified based on the available data (see Section 7.8.5).

The recommendation of this evaluation is that a CLH proposal is taken forward targeted to skin sensitisation, STOT RE and potentially environmental endpoints, if the registrants provide evidence that these classifications require reconsideration.

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

Not applicable.

4.1.3. Restriction

The high RCRs calculated by the eMSCA in its risk characterisation for human health, do not automatically signal an unacceptable risk. However, they do indicate there is a need for registrants to reconsider the operating conditions and risk management measures described in their CSRs to ensure that the measures they recommend provide adequate and sufficient protection and enough information is given in the eSDS to enable downstream users to understand what they need to do to manage the identified risks.

In the case of dermal exposure, given the skin sensitisation potential of TPP, there is a concern that if inadequate precautions are taken this could create a risk to workers' health. The eMSCA is proposing that as a first step, the harmonised classification for TPP should be updated to reflect the skin sensitisation hazard. The eMSCA assumes that this action will trigger registrants to reassess the OCs and RMMs they recommend to minimise skin exposure. These steps should be given sufficient time to take effect before further regulatory action is considered. After this time has elapsed, registrations should be re-evaluated to confirm how registrants are approaching the management of risks to workers. If this is deemed inadequate, the need for formal regulatory risk management action should be reconsidered.

4.1.4. Other EU-wide regulatory risk management measures

Not applicable.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

Not applicable.

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

Depending on the resource available the UKCA will try and make a start on a CLH dossier which will be handed over to the FR CA when the UK leaves the EU.

Table 3

FOLLOW-UP		
Follow-up action	**Date for intention**	**Actor**
Prepare a CLH dossier covering at a minimum skin sensitisation and repeat dose toxicity	*TBC*	*FR MSCA*

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

Triphenyl phosphite (TPP) was originally selected for substance evaluation in order to clarify concerns about the following:

- Human health: screening studies revealed adverse effects on reproductive, behavioural and neurotoxicity endpoints. The substance is a suspected reproductive toxicant and might possess endocrine disrupting properties (effects on adrenal glands, testes, kidney, brain).
- Human exposure: the substance is self-classified as a skin sensitiser and has wide dispersive use including consumer use and combined exposure. Exposure information and risk characterisation information is therefore missing; it is not possible to assess if the risks are being managed.
- Environment: the environmental fate properties of triphenyl phosphite (TPP) and related phenyl/alkyl phosphites generally include low water solubility, low vapour pressure, and rapid hydrolysis to phosphorous acid and corresponding alcohols (in the case of triphenyl phosphite it is phenol). As some phenols possess oestrogenic or endocrine-disruptor (ED) activities, there was a concern that the registered substance might be a potential ED (screening studies on TPP reported affected relative paired testes, adrenal glands, kidney and brain weights).

During the initial evaluation other concerns were also identified:

For human health, additional concerns related to repeated-dose toxicity and genotoxicity

For the environment, additional concerns related primarily to a lack of clarity over the expected rapid hydrolysis and the ready biodegradation of TPP and nature of its hydrolysis products. There were concerns over the methodology and reporting from the available abiotic and biotic degradation studies, which were performed under non-standard conditions owing to the low solubility and apparent rapid hydrolysis of TPP.

The outcome/conclusion of the evaluation of the endpoints of concern are briefly summarised in the table below.

Table 2

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
Human health; Reproductive toxicity, Neurotoxicity, Genotoxicity & Endocrine disruption	Concern not substantiated. No further action.
Human health; Skin sensitisation & Repeated dose toxicity	Available information is sufficient for classification. The eMSCA recommends that a CLH proposal for Skin Sens. 1A is taken forward. Additionally STOT RE 2; H373 (nervous system) should be included in the proposal.
Human exposure; Each of the exposure scenarios provided in registrations that were active during the initial assessment period (March 2013-14) and all additional information provided by the registrants during the decision making period and subsequent follow-up assessment was taken into account.	The eMSCA identified a need for registrants to provide more information in their exposure scenarios about the risk management measures required to use TPP safely. This information is listed in section 7.13.

Environmental concerns	The rapid environmental degradation of triphenyl phosphite to phenol has been confirmed through studies submitted in the lead Registrant's updated dossier. The potential endocrine disruption activity of TPP has been investigated predominantly through consideration of human health studies and ED information on phenol. These indicate no overall environmental ED concern for TPP.

7.1.1. Procedure

Initial evaluation period – March 2013-March 2014

The initial evaluation focussed on the information provided in the registration dossiers and some targeted literature searches conducted by the Registrant(s). The eMSCA met with the Registrant(s) in March 2013 to discuss the substance evaluation procedure and in October 2013 to discuss the initial outcomes of the evaluation. At various stages the Registrant(s) provided information following informal requests. The lead Registrant updated his registration dossier in March 2013 to include his own CSR; there were no other updates to the registration dossiers during the initial assessment period.

Chemistry and physico-chemistry

Analytical information provided in the dossiers was assessed to confirm substance identity and composition.

The physico-chemical data was screened, paying particular attention to those endpoints important to other parts of the evaluation, specifically water solubility, partition coefficient and vapour pressure.

Human health

The grounds for concern were the main focus of the human health assessment. However, a screen of all the available information was undertaken to identify other possible areas of concern. In particular, the combined repeated-dose toxicity study with reproductive toxicity screening test was thoroughly evaluated, since much of the information on mammalian toxicology in the registration dossier was provided by this one study. In addition, the need to request further information to determine if TPP was a genotoxicant was evaluated. The initial evaluation was based on information contained in the registration dossier. Where more detail was required, the original study reports were requested from the Registrant(s) and evaluated in full. These were: the combined repeated-dose toxicity study with reproductive toxicity screening test, an Ames test, DNA repair-damage assay and in vivo micronucleus assay.

Evaluation of the full study report of the combined repeated-dose toxicity study revealed additional information, from a 10-day range-finding study (not separately referenced) and the initial high-dose groups in the main study, which was not included in the dossier; the additional information has been included in this report. Additionally the Registrant(s) provided a list of published references on the neurotoxicity of TPP that was compiled in 2009. The eMSCA conducted an internet literature search to identify new information on the mammalian toxicology of TPP; this was conducted on ISI Web of Knowledge in July 2013 with the search terms: triphenyl phosphite, TPP, toxicology, toxicity and did not identify any new information.

Human exposure

For the human health exposure assessment, all the data provided by the Registrant(s) regarding exposure scenarios and exposure assessment were screened. It was determined

that further information would be required to complete the evaluation. Not enough information was included to run the ECETOC TRA (v2) exposure model with any degree of confidence and replicate the modelling estimates produced by the Registrant(s), nor to allow a decision to be made regarding any modifiers used in the Registrants' assessment.

Environment and environmental exposure

In addition to the original CoRAP grounds for concern, the initial environmental evaluation of the TPP dossier comprised a screen of all relevant available information in the dossiers. Given the Registrant's claim that TPP degrades rapidly in the environment, mainly to phenol, the eMSCA considered that an evaluation of environmental fate data was fundamental to the overall hazard and risk assessment of TPP. On request, the lead Registrant provided the full study reports for the original hydrolytic stability studies (to OECD test guideline (TG) 111) and ready biodegradation study (OECD TG 301D). The Registrant(s) had not undertaken any experimental ecotoxicological testing on TPP and a literature search conducted by the lead Registrant (not repeated by the eMSCA) did not identify any valid experimental toxicity endpoints for the substance. As no aquatic and terrestrial toxicity data were available to confirm the environmental hazard and risk assessment for TPP, the eMSCA referred to the available information, including PNEC values, already agreed in the phenol Risk Assessment Report (RAR), European Chemicals Bureau (2006)). The eMSCA did not re-run the exposure modelling calculations, but verified that the key input parameters used in the ECETOC TRA exposure modelling tool were appropriate and consistent with those agreed in the Risk Assessment Report for phenol. The eMSCA also considered the validity of the justifications for not conducting ecotoxicological testing on TPP itself.

The endocrine disruption (ED) potential of TPP was also addressed. As no environmental (including reproductive) ED effects data were available on TPP itself, the assessment was based on relevant Human Health ED information and that on phenol from the EU RAR (2006). Based on this, the eMSCA determined that there was no environmental ED hazard from TPP.

The eMSCA also identified a number of questions relating to the abiotic and biotic degradation potential of the substance and the studies that had previously been submitted to support this. This information was fundamental to the Registrant's proposal that TPP degraded so rapidly that the whole environmental assessment could be based only on its degradants, principally phenol. The eMSCA considered that additional information regarding environmental fate should be requested.

Unanimous agreement of the Member State Committee (MSC) was reached following discussion and modification of the draft decision at MSC-39 (December 2014). The final decision was sent to the registrants on 21 May 2015.

The registrants appealed the decision (A-005-2014) in August 2015 and in the Board of Appeal decision of 23 September 2015, ECHA's Executive Director partially rectified the decision. The registrants subsequently withdrew their appeal on 25 February 2016. The original deadline of 28 November 2017 was upheld in the partially rectified decision (dated 2 December 2015). The following information was requested;

- Genotoxicity

  a) Bacterial reverse mutation test to investigate the potential for DNA cross links/oxidative mutagenesis (test method EU B13/14, OECD 471) to include missing strains.

  b) In vitro micronucleus study (test method EU B.49, OECD 487);

- Further detailed information on human exposure

- Simulation Test - Aerobic Sewage Treatment, A: Activated Sludge Units, B: Biofilms (test method OECD 303A or B).

- Aerobic Mineralisation in Surface Water - Simulation Biodegradation Test (test method EU C.25/OECD 309)

- Further information on the available hydrolysis studies conducted in accordance with OECD 111 (in relation to the standard quality and reporting criteria).

Full details of the requests can be found on the ECHA website.

Follow-up evaluation – March 2018 – March 2019

The registrants submitted an updated dossier on 28 November 2017 but the submission failed. An update submitted on 22 March 2018 was accepted.

Human health

The registrants conducted the requested genotoxicity tests; the complete study reports for both studies were provided to the eMSCA, and were evaluated in full. See section 7.9.5 for detail.

Additional human exposure information was provided. This is discussed in section 7.15

Environment and environmental exposure

The Registrant(s) had previously indicated their intention to waive these requirements and address the concerns in an alternative way. Instead of submitting the above information, the Registrant(s) provided two new modified abiotic and biotic degradation studies on TPP. These were:

Unpublished (2017c). Triphenyl phosphite: An evaluation of hydrolysis as a function of pH (OECD TG 111).

Unpublished (2015). Biodegradability of triphenyl phosphite in the closed bottle test method (OECD TG 301D).

Along with the questions raised in the initial evaluation, these new studies are considered fully in Section 7.7.1 to conclude on whether the environmental fate of TPP, and any resulting hazards and risks, have been fully addressed.

7.2. Identity of the substance

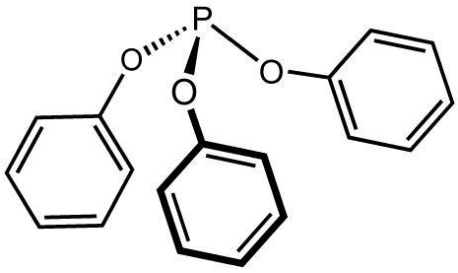
The following identity information is reported on the ECHA dissemination site.

Table 3

SUBSTANCE IDENTITY	
Public name:	Triphenyl phosphite
EC number:	202-908-4
CAS number:	101-02-0
Index number in Annex VI of the CLP Regulation:	015-105-00-7
Molecular formula:	$C_{18}H_{15}O_3P$
Molecular weight range:	310.29
Synonyms:	TPP Trade names: Weston TPP, Mark CH 66, Triphenyl phosphite, ADK STAB TPP, Lankromark LE65, Rostabil TPP, Doverphos 10

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

Structural formula:



7.3. Physico-chemical properties

The information provided comprised a mix of modern studies using acceptable methods, modelled and literature data. However, limited information was reported in the IUCLID dossier and the registrants should consider adding more detail.

Three physico-chemical properties are needed for the purposes of this evaluation and are described in more detail below.

Water Solubility:

Three values are provided, two are estimates based on calculations (assigned a reliability of 2 by the registrant) and the third is a literature value (Handbook of Chemistry and Physics, CRC Press) (reliability 4).

Results from the WATERNT v1.01 and WSKOW v1.41 models from EPISUITE v4.00:

WATERNT = 0.002 mg/L
WSKOW (based on estimated Kow of 6.62). = 0.02 mg/L
Literature value (CRC handbook) = 0.3 mg/L

The three values quoted have a range over 3 orders of magnitude (reported at 25°C) and consequently TPP could be described as slightly soluble (0.1-100 mg/L) or insoluble (<0.1mg/L).

The registrant has not justified why the modelled values should be used over the literature value. However, as the substance hydrolyses rapidly (DT50 <1 day) a measured value is unlikely to provide a more reliable result.

Partition Coefficient:

Two calculated values for log Kow are provided:

KOWWIN v 1.67 = 6.62 at 25°C
ACD software = 7.39

The registrant has indicated that it is not possible to measure the partition coefficient owing to the rapid hydrolysis. A measured value is unlikely to provide a reliable result.

Vapour Pressure:

An experimental value of ≤0.069 Pa at 25°C was obtained using the Effusion method (vapour pressure balance).

The registrant also provided a calculated value:

EPISUITE 4.0(MPBPWIN v 1.43), modified grain method = 0.0102 Pa at 25°C

A low vapour pressure would be expected given the high boiling point of the substance.

The physico-chemical properties reported in the registration dossiers are summarised in Table 4.

Table 4

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	Liquid at 20°C and 101.3 kPa
Melting/freezing point	25°C
Boiling point	386°C at 101.3 kPa
Relative Density	1.18 at 20°C
Vapour pressure	≤0.069 Pa at 25°C
Water solubility	0.002 to 0.3 mg/L at 25°C
Partition coefficient n-octanol/water (Log Kow)	Estimated Log Kow: 6.62
Flash point	172°C
Flammability	Non-Flammable
Self ignition temperature/ Auto flammability	>400°C
Viscosity	8.06 mm^2/s at 40°C

7.4. Manufacture and uses

7.4.1. Quantities

The aggregated tonnage information as given on the ECHA dissemination site (http://echa.europa.eu/web/guest/information-on-chemicals/) is highlighted in table 5.

Table 5

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

7.4.2. Overview of uses

7.5.2.1. Manufacture

Triphenyl phosphite (TPP) is an alkyl aryl phosphite. It is typically manufactured in batches by reacting phenol with phosphorus trichloride in a closed system. Table 6 lists the uses identified on ECHA's dissemination site for TPP.

Table 6: Disseminated uses for triphenyl phosphite

USES	Use(s)
Use as intermediate	Use as an intermediate in chemical manufacture Lubricant manufacture
Formulation	Use as antioxidant stabiliser in polymers (PEST GES 1-2) Manufacture of coatings and adhesives Formulation, packing and distribution
Uses at industrial sites	Use of coatings and adhesives Use of Formulated Polymer in Manufacturing (PEST GES 3-6) Industrial use of lubricants in open systems*
Uses by professional workers	Professional use of lubricants including in open systems* Professional use of coatings and adhesives*
Consumer Uses	Consumer use of lubricants* Consumer use of coatings and adhesives*
Article service life	Manipulating polymer articles containing TPP covering the following article categories: • rubber articles • plastic articles Manipulating articles with coatings containing TPP covering the following article categories: • machinery, mechanical appliances, electrical/electronic articles

*although these uses are listed in the information ECHA was disseminating from registrations in January 2019, in 2015, the Phosphites Stabilisers REACH Consortium obtained information indicating that these uses do not occur.

The primary use of TPP is as an intermediate in the manufacture of other substances, most notably alkyl-phenyl phosphites such as diphenyl isodecyl phosphite (DPDP) and diisodecyl phenyl phosphite (DDPP). This use is performed predominantly under strictly controlled conditions (information provided by the Phosphites Stabilisers REACH Consortium (PSRC) based on a survey conducted in 2015 indicated that at that time, at least two thirds of the aggregated tonnage supplied to the EU market was used as an intermediate under SCC). However, a minor percentage of the total TPP supplied to the EU market is used as an intermediate under more open conditions, this includes its use in the manufacture of lubricants. TPP is also used as an antioxidant and UV stabiliser in non-food contact polymers including polyurethanes (to reduce scorching during curing), styrenics, polyesters (to control viscosity and colour), epoxies, PVC and polycarbonates, coatings and adhesives[4,5,6,7,8]. The typical amount of TPP in a formulated polymer/coating is less than 5% and in many cases may be less than 1%.

When TPP was first registered in 2010, scenarios were produced covering professional and consumer use of lubricants, coatings and adhesives containing TPP. Information obtained by the Phosphite Stabilisers REACH Consortium (PSRC) in 2015 indicates that TPP is transformed into another substance during the manufacture of lubricants and is therefore not present in the final lubricant. Also, TPP containing coatings and adhesives are not supplied for professional or consumer use. Since professional and consumer uses are still listed on ECHA's dissemination site, it is likely that some registrations continue to report these uses.

Note to registrants: To ensure accurate information is available to authorities in relation to the uses and the conditions of use that are supported, all registrants should ensure that they update their CSRs promptly when they receive new information. The comments provided by the eMSCA in this report about the use and exposure information presented in registrations constitute new information. All registrants, including those whose registrations were not included in this evaluation, should ensure (subject to tonnage requirements) that an exposure scenario is available for each of the uses that they cover in their registration and should take account of the findings from this substance evaluation in their own chemical safety assessments.

Other substances containing triphenyl phosphite as a constituent/impurity

Other registered substances may contain TPP as an impurity. Table 7 contains a list of such substances which were identfied during the substance evaluation using publicly available information. A systematic search of all registrations has not been performed therefore this list may not be comprehensive. A consideration of these sources of exposure is outside the scope of this evaluation. However, when considering possible background exposure to TPP (or its breakdown products) it is important to be aware of these additional potential sources.

---

[4] https://www.ulprospector.com/en/na/Adhesives/Detail/23490/556951/Doverphos-10-TPP (accessed January 2019)

[5] http://www.valtris.com/product/lankromark-le65-tpp/ (accessed January 2019)

[6] https://www.brenntag.com/media/documents/bsi/product_data_sheets/material_science/addivant/weston_tpp_pds.pdf (accessed January 2019)

[7] https://www.products.pcc.eu/en/id/1107/rostabil-tpp/ (accessed January 2019)

[8] https://vestachem.com/chemicals/triphenyl-phosphite/ (accessed January 2019)

Table 7 - Other substances containing TPP as a constituent/impurity

Substance (*synonym*)	Abbrevi[p]	EC	CAS	Registration status[9]	Percentage TPhP
2-ethylhexyl diphenyl phosphite	EHDPP	239-716-5	15647-08-2	2 registrants, tonnage band 100 – 1 000 tpa.	All compositions listed on ECHA's dissemination site report the presence of TPP. No information on percentage composition is reported.
Isodecyl diphenyl phosphite	DPDP	247-777-4	26544-23-0	7 joint registrants, tonnage band 1000 – 10 000 tpa	Some compositions listed on ECHA's dissemination site report the presence of TPP. No information on percentage composition is reported.
Diisodecyl phenyl phosphite	DDPP	247-098-3	25550-98-5	9 joint registrants, tonnage band 1000 – 10 000 tpa	Some compositions listed on ECHA's dissemination site report the presence of TPP. A Canadian draft screening assessment of alkyl aryl phosphites reports the presence of 2% w/w TPP[10] .

7.5. Classification and Labelling

7.5.1. Harmonised Classification (Annex VI of CLP)

TPP is listed with the following harmonised classification in Annex VI of Regulation (EC) No 1272/2008 (index number 015-105-00-7).

Table 8

HARMONISED CLASSIFICATION ACCORDING TO ANNEX VI OF CLP REGULATION (REGULATION (EC) 1272/2008)							
Index No	**International Chemical Identification**	**EC No**	**CAS No**	**Classification**		**Spec. Conc. Limits, M-factors**	**Notes**
				Hazard Class and Category Code(s)	**Hazard statement code(s)**		
015-105-00-7	Triphenyl phosphite	202-908-4	101-02-0	Eye Irrit. 2 Skin Irrit. 2 Aquatic Acute 1 Aquatic Chronic 1	H319 H315 H400 H410		

[9] Registration status based on information published on ECHA's dissemination site in January 2019.
[10] http://www.ec.gc.ca/ese-ees/D02DDD1D-6E67-44E1-BBFD-1F5A5E3819D8/AAPhosphites_dSAR_EN.pdf (site accessed January 2019)

7.5.2. Self-classification

In addition to the harmonised classification given in table 8, the registrants also apply the following self-classification:

Acute Tox 4; H302
Skin Sens 1; H317
STOT RE 2; H373

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

Table 9

Classification	Hazard Statement
Acute Tox. 4	H302
Acute Tox. 4	H332
STOT RE 2	H373
STOT SE 2	H371
Skin Sens. 1	H317
Skin Sens. 1A	H317
Skin Sens. 1B	H317
Skin Corr. 1B	H314

7.6. Environmental fate properties

A number of unpublished studies were included in the registration dossier (as robust study summaries), and have been used during the evaluation. Full references are not given in this report.

7.6.1. Abiotic degradation

7.7.1.1. Hydrolysis

Three studies have been referenced on the hydrolysis of TPP. The first two considered during the initial evaluation period (2013-14) are an experimental study (Unpublished, 2002) and a publication by Al-Lohedan (1991). A new study (Unpublished, 2017c) was subsequently included in the updated dossier. Details of all these studies are provided below:

i) The earlier experimental studies (Unpublished, 2002) were conducted and reported in accordance with GLP. The Report cites two individual studies conducted at different pH (one at pH 5-6 and another at pH 9). It was originally attempted to conduct a hydrolysis study according to the standard OECD 111 protocol (hydrolysis as a function of pH). However, owing to the poor solubility of the test substance (0.002 - 0.3 mg/L at 25 °C, see Section 7.4) and its rapid hydrolysis at the limit of solubility, the OECD Guidance Document 23 on 'Aquatic Toxicity Testing of Difficult Substances and Mixtures' (OECD (2000)) was consulted. This low water solubility of TPP precluded a standard direct injection analytical method as was determined by the injection of near-saturated TPP solutions in 1% acetonitrile buffers which showed insufficient HPLC responses. A more time-consuming extraction method would have been required for analysis of TPP in aqueous solutions and the study authors considered this likely to produce erroneous results owing to its rapid hydrolysis during the extraction procedure.

Performance of the standard OECD hydrolysis test was, therefore, considered not to be technically feasible under normal laboratory conditions. Because of this, some necessary

adaptations and non-standard analytical methods were employed because, according to OECD 111, the test substance 'must be sufficiently soluble in test buffers to be detected by the analytical method'. Co-solvents were therefore used to solubilise the TPP so it could be analysed in the mixed aqueous phase. The HPLC method used in these studies was also based on alternative analytical methods in published reports (Baylocq et al, 1986; Stevenson et al, 1999; Stevenson, 1997; Munteanu et al 1985 were cited in the study report). The sensitivity of these methods in relation to the analytical criteria given in OECD 111 is not stated however and should ideally have been reported. Give the nature of the solubility and hydrolysis of TPP, these deviations in analytical method are considered appropriate and the Registrant(s) proposed that the study was 'reliable without restriction' (Klimisch 1). The eMSCA considers it should be Klimisch 2 'reliable with restrictions' given the uncertainty over the analytical methods used.

These unpublished hydrolysis studies (2002) also used a large amount of co-solvent (up to about 50%); this is significantly above that proposed in OECD 111 ('should not normally exceed 1% v/v'). However, where a higher concentration of solvents is used (e.g. in the case of poorly soluble test substances), this can be permitted when it is shown that the solvent has no effect on the hydrolysis of the test substance. There is a concern however, that the co-solvent may act as a 'sink' for adsorption of the TPP or in other ways might itself influence the apparent hydrolysis rate. Evidence on this point or the need for such high solvent levels is not clear from the RSS. However, the original study reports have been evaluated and the authors suggest the TPP hydrolysis reaction would be faster in the absence of co-solvent because of the higher water concentration. It is postulated in the report that half-lives of TPP in pure water would actually be less than the quoted 0.5 and 14 hours (at 22 °C).

No further methodological detail is available from the RSS, but the original study reports have been consulted and the key results are provided below:

Table 10. Summary of hydrolytic half-lives of TPP in unpublished experimental studies (2002)

Aqueous Solvent	Cosolvent	Temp (°C)	Rate Constant	Half-life (h)[a]
Deionised water; initial pH 6-7	Methanol (50%)	22	NA[b]	~ 0.5
pH 9 buffer	Acetonitrile (50%)	22	$1.3E^{-5}$ s^{-1}	14

[a] This is the estimated (pseudo-)first order half-life (= DT50) in the absence of cosolvent. Confidence limits not reported.

[b] Not available from the data - estimated at 1.52 h^{-1} only from 2-point graphical plot

In summary, the results of experimental studies (Unpublished, 2002) on aqueous/co-solvent TPP solutions indicated that half-lives in deionised water at pH 6-7 and pH 9 were approximately 0.5 hours and less than 14 hours respectively at 22 °C.

ii) The published paper by H. A. Al-Lohedan (1991) reported a TPP hydrolysis half-life of 1.1 hours in water at a very low pH of 1.3 and 25 °C by extrapolation of results on TPP stability in solutions of ethanol and water. As the actual study report is not available, the methodology and results cannot be verified, nor the reliability of the study or whether it was conducted in accordance with GLP. The eMSCA proposes it is Klimisch 4: 'Not assignable'; the tabulated results are presented below however.

Table 11. Summary of hydrolytic half-life of TPP (Al-Lohedan (1991))

Aqueous Solvent	Cosolvent	Temp (°C)	Rate Constant	Half-life (h)[a]	Source
Aq. HCl; pH 1.3	- [b]	25	$1.8E^{-4}$ s^{-1}	1.1	Al-Lohedan (1991)

[a] This is the estimated (pseudo-)first order half-life (= DT50) in the absence of co-solvent, confidence limits not reported
[b] Half-life extrapolated to pure water from results on ethanol/water mixtures

iii) Following the initial 2013-14 evaluation and the issuing of ECHA's Decision on TPP on 2 December 2015, the Registrant's dossier was updated to include an RSS for a further hydrolysis study (Unpublished, 2017c) - 'Triphenyl phosphite: An evaluation of hydrolysis as a function of pH'. The study report has also been made available to the eMSCA and a summary evaluation of it is provided below:

Methodology

The study was conducted in accordance with OECD Test Guideline 111, and it was GLP compliant. One exception to the guideline was that verification of the stability of the test substance and analytical standard under the storage conditions at the test site were not determined prior to their use in the study. However, it is generally assumed that a substance will remain stable in storage for two years and the test substance was manufactured on 12 December 2016 and used by 30 August 2017.

Experimental conditions were established based on previous non-GLP range-finding experiments which triggered a Tier 2 study. The Tier 2 test was conducted at 20 °C to determine the rate of hydrolysis of the test substance in aqueous media in the pH range of 4 to 9 and at 12 °C for pH 7. The test substance was triphenyl phosphite with a purity of 98.3% w/w. Solutions of aqueous buffers were prepared at pH 4, pH 7 and pH 9, using a 0.1 M acetate, 0.01 M 3-(N-morpholino)propanesulfonic acid (MOPS) and 0.01 M 3-aminopropanesulfonic acid (TAPS) buffer, respectively. The presence of 2 mM final concentration of ammonium acetate in the buffer (along with the nitrogen atoms of the TAPS molecules) was designed to help reduce possible non-specific binding of silanol groups of silica gel with TPP and potential hydrolysis degradants.

Since the test substance is a dense liquid and poorly soluble in water, silica gel was used as a carrier to help disperse the test substance in the test system. This choice was based on an assessment of preliminary studies of different approaches for dosing TPP including:

1) adding the TPP to buffer using 1% acetone and vigorously agitating the test systems during incubation,
2) presenting the TPP as a thin film on the inner walls of the test vessels using a solvent and vigorously agitating the test systems during incubation and
3) applying the TPP to silica gel using solvent and incubating the test systems with gentle mixing. The most rapid and extensive hydrolysis was observed when TPP was dosed using silica gel.

TPP had been visually observed dropping out of solution when added in a small volume of acetone to buffer solutions and subsequently aggregating into larger droplets, this probably explains the less rapid and less extensive hydrolysis observed in the first two treatments. Consequently, dosing with silica gel was used for the definitive hydrolysis study after verifying that TPP did not hydrolyse on silica gel in the absence of water.

This use of silica gel is a modification of the standard guideline which normally states that the substance should be applied as an aqueous solution. However, it is considered an appropriate adaptation given the very low solubility of the test substance. Although not specifically mentioning silica gel, such adaptations (such as higher than normal solvent levels) to increase availability for hydrolytic reactions are mentioned in OECD TG 111, as long as they do not in themselves cause or inhibit hydrolysis.

The test vessels (two replicates for each treatment and control groups per sampling interval) were glass vials with a volume of approximately 24 mL containing 0.15 g of silica gel, which was dried for approximately 2 hours inside an oven set at approximately 105 °C. For each test vessel containing the silica gel, 250 µL of 558 mg/L triphenyl phosphite

(TPP) stock solution in anhydrous acetone was added, exceeding the 1 % v/v guideline for the use of miscible solvents. However, the acetone was evaporated under a stream of nitrogen gas before the experiment was initiated by adding 24 mL of sterile (abiotic) buffer solution to each test vessel. The final nominal concentration of TPP in each test vessel was 5.81 mg/L, this is far above the water solubility of TPP and was only possible due to the silica gel. In the control vessels (two replicates per sampling interval) used to determine the effect of silica gel on possible TPP hydrolysis, 24 mL of anhydrous acetonitrile was added to each vessel to initiate the hydrolytic reaction. The test vessels were sealed with UV light-sterilized aluminium-lined caps and wrapped with Parafilm® and placed on a rotator inside a temperature-controlled incubator to keep the silica gel suspended during the hydrolysis experiments. TPP was not itself analysed for but the course of its hydrolysis was monitored by quantifying dissolved phenol (the major water soluble hydrolytic product) in the buffer at different sampling intervals.

At selected sampling intervals, duplicate test vessels for each treatment were removed from the incubator. After allowing the silica gel to settle for approximately 5 minutes, a 0.5 mL aliquot of the supernatant was taken from each vessel and mixed with 0.5 mL of acetonitrile (ACN) for quantifying phenol by a high performance liquid chromatography (HPLC) system equipped with a UV light detector set at wavelength of 267 nm. Phenol with a purity of 99.98% was used in HPLC standard solutions for quantifying phenol production. The level of quantification (LOQ) for phenol in sample solutions was 0.25 mg/L. For the anhydrous ACN control, no phenol concentrations were detected above the LOQ in all samples during the course of TPP hydrolysis. To estimate the background levels of residual phenol in anhydrous ACN samples dosed with TPP therefore, manual integrations were applied to baseline-resolved phenol chromatographic peaks with chromatographic peak areas below the LOQ to extrapolate phenol concentrations. No kinetic analysis was performed on the anhydrous ACN control samples since there was virtually no hydrolysis of TPP over 7 days of incubation at 20 °C. The time course of phenol formation in the other treatment groups was plotted graphically and curve-fitted to estimate the rate constants and first order half-lives (DT_{50}) of TPP hydrolysis. Sterility and pH (within ±0.1) of the samples were maintained during the study period (there was a minor deviation as pH changed by 0.12 in the treatment group at pH 9). The recorded temperatures were also within the specified range of 20 ± 0.5 ºC and 12 ± 0.5 ºC, respectively.

Results

It was not possible to calculate mass balances and recoveries as only phenol was quantified. The test substance TPP was not quantified itself and methods to measure the concentration of TPP were not described in the study report, instead nominal concentrations of TPP in stock solution and in each vessel were used. It is not known whether these nominal concentrations were achieved. Chromatographic peaks for TPP were however recorded and were limited to the acetate buffer at 20 °C and MOPS buffer at 12 °C in which TPP hydrolysis was less rapid. Plots showing concentration versus time were included for the major hydrolysis product phenol, and not for the test substance. The concentration of phenol over time was also not log-transformed on these graphs. However, as the hydrolysis of TPP is a straightforward conversion with only very temporary intermediates, this approach to quantify hydrolysis by analysing phenol is considered appropriate. The study provided evidence for this argument as no other peaks from HPLC analyses were observed in the samples that would correspond to other potential intermediate hydrolytic products, such as mono- and diphenyl phosphite.

The main results of the study are summarised in the table below. These show that the rate constants of TPP hydrolysis to form phenol were pH dependent, with the highest rate of 1.6044 $hour^{-1}$ occurring at pH 9 and lowest rate of 0.0316 $hour^{-1}$ occurring at pH 4. The rate constant under pH 7 at 20 °C was estimated to be 0.1065 $hour^{-1}$. At 20 °C, the estimated first order half-lives (DT_{50}) of TPP in abiotic buffer solutions were 21.9, 6.5, and 0.43 hours, respectively at pH 4, 7, and 9. At 12 °C, the DT_{50} of TPP in abiotic buffer solution at pH 7 was 14.7 hours, which is about 2-fold longer than that at 20 °C. The

measured half-life at 12 °C (14.7 h) was stated to be comparable to a 12.2 hour half-life at 12 °C estimated from the 20 °C data using the Arrhenius equation.

Only approximately 1.9 molar percentage (mol%) of phenol was observed in anhydrous ACN over 168 hours at 20 °C, which is 0.8 mol% above the background level (1.1 mol%) of residual phenol detected in TPP used for the testing. These observations indicate that the vast majority of phenol formed with time in the four treatment groups resulted from TPP hydrolysis. Confidence intervals were not presented for kinetic parameters correlation coefficients, rate constants and DT_{50}, although standard deviations were presented for average phenol concentrations at each sampling interval.

Table 12. Summary of hydrolytic half-lives of TPP in experimental study by Unpublished (2017c)

Treatment Group	Buffer	Temperature (°C)	Incubation Time (hours)	Maximum Phenol Yield (mol%)	First Order Rate Constant ($hour^{-1}$)	DT_{50} (hours)	$R^{2\ddagger}$	*P* value§
1	pH 4.09	20	120	43.4	0.0316	21.9	0.9523	< 0.001
2	pH 7.05	20	53	78.0	0.1065	6.5	0.9832	< 0.001
3	pH 7.03	12	77	78.0	0.0472	14.7	0.9930	< 0.001
4	pH 8.99	20	27	84.1	1.6045	0.43	0.9515	< 0.001
5 (Control)	Anhydrous ACN	20	168	1.90	N/A	N/A	N/A	N/A

‡: Square of correlation coefficient of curve-fit function.

§: Statistical *P* values were obtained from curve-fitting and kinetic analysis of phenol concentrations versus incubation time graphs (Appendix IV).

N/A: Not applicable; TPP was virtually not hydrolyzed in anhydrous ACN containing silica gel.

For treatment group 1 at pH 4.09 and 20 °C, the initial rate of TPP hydrolysis was near linear and a maximum phenol yield of 43.4 mol% was reached at 72 hours sampling interval and phenol yield then levelled off thereafter. The Registrant stated that this reduced yield would be consistent with partial hydrolysis of the parent or more limited hydrolysis of monophenyl and diphenyl phosphites under the acidic pH condition. In contrast, a maximum phenol yield of 78.0 mol% was observed at 45 and 77 hours sampling intervals in the pH 7.05 treatment at 20 °C and pH 7.03 treatment at 12 °C, respectively. The maximum phenol yield of 84.1 mol% was observed at 4 hours under pH 8.99 at 20 °C. The Registrant stated that these yields are consistent with extensive hydrolysis of tri-, di and monophenyl phosphites.

<u>eMSCA conclusions on unpublished hydrolysis study (2017c)</u>

This hydrolysis study on TPP was conducted to OECD Guideline 111 and in compliance with GLP. The main modification was the use of silica gel as a carrier for the poorly soluble test substance. There was no quantification of the test substance and no calculation of mass balance and recoveries. However, since hydrolysis was effectively determined through production of the main hydrolytic product, phenol, these deviations can be accepted. Overall, the study results indicate that TPP can be readily hydrolysed to phenol under different pH and temperature conditions, if the test substance is available for hydrolytic reactions. It is proposed, and the eMSCA agrees, that this study is Klimisch reliability score 1 (reliable without restriction).

7.7.1.1.1. Overall summary and conclusions regarding hydrolysis

Despite some uncertainty over the analytical methods and the amount of co-solvent used, the original hydrolysis study (Unpublished, 2002) provides information to support the rapid hydrolysis of TPP particularly at neutral pH. It reported half-lives in deionised water at pH 6-7 and pH 9 of approximately 0.5 hours and less than 14 hours respectively at 22 °C. According to OECD 111 any major hydrolysis products (at least those representing ≥10 % of the applied dose) should be identified by appropriate analytical methods. There is evidence from the analytical data presented in this unpublished report (2002) of significant amounts of phenol being formed in direct correlation with the decline in TPP. This adds weight to the hydrolysis and degradation pathway proposed by the lead Registrant. Whilst no hydrolytic pathway specifically for TPP was found in the chemical literature, public literature on other organic phosphites was referenced in the unpublished report (2002). This supported a pathway for TPP in which it hydrolyses to phenol and phosphorous acid via possible di- and mono-ester hydrolysis intermediates. Other literature reported however, that the hydrolysis of TPP proceeds directly to phenol and phosphorous acid. This view was supported by other experimental evidence reported in Unpublished (2002) where no significant peaks for intermediate degradants such the di-ester were observed. Overall therefore, literature and experimental evidence supports the direct hydrolysis of TPP to phenol and phosphorous acid, with little or no accumulation of the di- and mono-ester hydrolysis products.

The published paper by Al-Lohedan (1991) reported a TPP hydrolysis half-life of 1.1 hours in water at a very low pH of 1.3 and 25 °C by extrapolation of results on stability of TPP solutions in ethanol and water. As there is little methodological detail and the actual study report is not available, these results cannot be verified. It does add weight to the rapid hydrolysis conclusion, although only at an unrealistically low pH.

The most recent reliable study (Unpublished, 2017c) also indicates rapid hydrolysis of TPP under conditions where solubilisation and exposure of TPP to hydrolytic reactions is facilitated through the use of an inert silica gel carrier. Such an adaptation is considered reasonable given the low solubility and apparent hydrophobicity of the test substance. At 20 °C and pH 4, 7 and 9, the half-life of TPP was 21.9, 6.5, and 0.43 hours respectively. At 12 °C and pH 7, the half-life of TPP was 14.7 hours. This study also indicates that the hydrolysis of TPP is a straightforward conversion to phenol with only very temporary intermediates.

Overall, based on the results of experimental and previous published work, TPP appears to hydrolyse rapidly in water, with half-lives between 0.5 to 6.5 hours at neutral pH and 20-25°C. This increased to 14.7 hours at 12°C in the Unpublished (2017c) study, however this is still less than 1 day. Regarding the hydrolytic pathway, the literature and experimental data provided indicates that TPP hydrolyses essentially completely to phenol with little or no accumulation of possible di- and mono-ester hydrolysis products or oxidation products.

Supplementary information regarding oxidation:

Further to enquiries made by the UK CA, the lead Registrant provided the following information in relation to whether triphenyl phosphite could oxidize under environmental conditions to form triphenyl phosphate (as opposed to hydrolysing to the alcohol (i.e. phenol and phosphorous acid), triphenyl phosphate is a substance of concern in the environment due to potential endocrine disruption effects. The Registrant's response is summarised below:

"*Following a discussion on this issue with a Ph.D. chemist from one of the TPP co-Registrants, he indicates that under ambient temperature and conditions (i.e. humidity/water) TPP would only be expected to hydrolyze to phenol and phosphorous acid. This is consistent with the water solubility and hydrolysis data we have in the dossier. We*

believe this information supports the approach that we took with the environmental assessment and significant oxidation to triphenyl phosphate is considered unlikely under normal environmental conditions."

To support the above assertion and the lack of significant oxidation to triphenyl phosphate, the Registrant(s) should ideally provide supporting experimental clarification under more oxidative conditions than occurred in the available tests (e.g. using aeration). However, given the hydrolysis seen under slightly acid, neutral as well as alkaline aerobic conditions, as well as the lack of formation of any significant degradants other than phenol and phosphorous acid, significant oxidation is considered unlikely.

7.7.1.2. Phototransformation/photolysis

7.7.1.2.1. Phototransformation in air

The lead Registrant has referenced a QSAR Study Report on TPP generated using EPIWIN (v3.10)\AopWin v.1.90 and conducted in 2004.

The principle of this modelling method is that atmospheric oxidation is estimated using the EPIWIN hydroxyl radical reaction type. The model assumes a 12-hour day; a hydroxyl concentration of 1.5×10^6 OH/cm^3; a Rate Constant of 10.8423×10^{-12} cm^3/ molecule-sec; a dissipation half-life of 0.99 days; and a temperature of 25 °C.

The lead Registrant considers the study to be 'reliable with restrictions' (Klimisch 2). No information on the suitability of this particular model or how TPP fits within its applicability domain has been presented. Although the modelling has not been re-run, the input parameters appear correct and the eMSCA considers this reliability score to be appropriate for such a QSAR estimate.

Results of the modelling indicate that photolysis is not anticipated to be a major degradation pathway for TPP, although photo-oxidation via hydroxyl radical reaction could theoretically occur with any TPP in the air having a modelled dissipation half-life of 0.99 days. TPP also has a very low vapour pressure (0.069 Pa at 25 °C from Section 7.4) and so it is not expected to partition to the atmosphere to any significant extent.

7.7.1.2.2. Phototransformation in water

No information submitted and not considered necessary for this evaluation.

7.7.1.2.2. Phototransformation in soil

No information submitted and not considered necessary for this evaluation.

7.7.2. Biotic degradation

7.7.2.1. Biodegradation in water

7.7.2.1.1. Estimated data

No modelling information was supplied as experimental data are available.

7.7.2.1.2. Screening tests

Two studies are available of the biodegradation of TPP. The original dossier evaluation in 2013-14 had access only to one experimental screening test for biodegradation of TPP in water (Unpublished, 2003). Following the ECHA Decision in 2015, a further experimental

study (Unpublished, 2015) was included in the updated dossier. These are evaluated below:

i) In the unpublished study (2003) a sample of triphenyl phosphite (TPP, >95% pure, exact purity confidential) was tested to assess its ready biodegradability using the procedure outlined in the OECD 301D Closed Bottle Test. Biodegradability was assessed by measuring the biological oxygen demand (BOD) of a microbial population (secondary effluent inoculum taken from a domestic wastewater treatment plant (WWTP) in Richmond, US. containing 9.0×10^4 cells/L) exposed for 28 days to the test substance under controlled aerobic conditions. This BOD was compared with the theoretical oxygen demand (ThOD) of the test substance.

All phases of this study were stated to have been conducted according to GLP standards. There were some deviations from the study plan, such as changes to the sampling and analysis owing to rapid hydrolysis of TPP (discussed further below). The incubation temperature also ranged widely from 10 to 24 °C rather than 20 ± 1 °C; A study plan deviation for this change was included in an Appendix A to the study report and it was stated that this deviation should not to have significantly affected the results. This is also discussed further below.

The initial nominal test substance concentration was 10 mg/L, which is substantially above the stated limit of water solubility. A series of five test solutions were used in the test: an inoculum blank determined the biological oxygen demand in the absence of either the reference or test substances. A filter paper control was used to monitor the effect of the filter paper on the inoculum and to provide the blank oxygen uptake values for bottles containing test substance and filter paper. A reference substance (sodium benzoate, CAS No. 532-32-1) is classified as readily biodegradable and was used as a positive control to assess test validity. A toxicity control contained bottles of both test and reference substances and was used to determine if the test substance inhibited inoculum metabolism. There were two replicates per treatment. Owing to expected problems with adsorption to surfaces and rapid hydrolysis, measured aliquots of the test substance were added directly to the test bottles instead of making stock and then batch solutions.

Dissolved oxygen concentrations and water temperature in bottles from each test series were sampled in duplicate on pre-assigned days. Cumulative degradation was plotted versus time to visually assess the rates at which the test substance and the reference substance were degrading. Significant differences in mean dissolved oxygen concentrations between the two controls (inoculum blank and filter paper blank) and percent degradation between the reference substance treatment and toxicity control were assessed with the Wilcoxon paired sample test. Analytical confirmation of the concentration of test substance in the test solutions was not conducted because the test substance was expected to hydrolyse during any analytical procedure. The standard validity criteria for this test (in terms of differences between replicates, oxygen uptake by the inoculum blank and filter paper controls, as well as differences in percent degradation between the reference substance and toxicity control) were fulfilled. Any other deviations were felt by the authors to be appropriate for such a rapidly hydrolysing substance.

No further methodological information is available from the RSS, although the original study report has been consulted for additional detail. The key results were reported in the study and dossier as follows:

Table 13. Results in terms of percent degradation of TPP (Unpublished (2003))

Sampling time	Parameter	% degradation	Std. deviation
3 d	O2 consumption	0.54	-
7 d	O2 consumption	1.46	-
18 d	O2 consumption	0.45	-
24 d	O2 consumption	2.46	-
28 d	O2 consumption	0.14	-

Table 14. Mean Percent Degradation (%) of test and control substances

Day	Test Substance	Reference Substance	Toxicity Control
3	0.54	--	--
7	1.46	84.13	84.43
10	-0.43	--	--
14	-0.86	86.23	66.32
16	-0.14	--	--
18	0.45	--	--
21	-0.18	86.38	64.07
24	2.36	--	--
28	0.14	82.04	79.49

The results of the experimental screening study (Unpublished, 2003) are assumed to relate to TPP and its hydrolysis products, although no information was provided on these hydrolysis products and the speed, levels and proportions in which they were formed in this test. Adsorption to surfaces and the complex test medium could have limited hydrolysis compared to that seen in the standard OECD 111 hydrolysis tests at Section 7.7.1.1. Percent degradation for the 'test material' did not reach 60% in a 10 day window within the 28 day test period, and it only reached around 0.1% by the end of the test, indicating that the TPP and its hydrolysis products were not readily biodegradable. There was no significant difference in percent biodegradation between the reference substance treatment and the toxicity control (Wilcoxon paired-sample test, $p > 0.05$) indicating that the test substance was non-inhibitory.

In summary, the test compound TPP (plus any hydrolysis products) was determined to be not readily biodegradable when tested according to OECD 301D. Poor water solubility, and rapid hydrolysis once any TPP did dissolve, were assumed in this test but not reported in detail (there was no chemical analysis).

Given the significant temperature variation, the study was previously considered to be 'reliable with restrictions' (Klimisch 2). In their most recent dossier update, the lead Registrant has since downgraded this study to 'not reliable' (Klimisch 3). In their reasoning for this they state that that there were major methodological deficiencies and '... *the study methods were inadequate to ensure the test material was bioavailable to the inoculum. As such, the results of this study have been disregarded*...'.

ii) The more recently submitted biodegradation study referenced in the updated dossier is Unpublished (2015): 'Biodegradability of triphenyl phosphite in the closed bottle test method (OECD TG 301)'. This was performed according to OECD test guideline 301 D: Closed Bottle Test and in compliance with GLP. The test substance was TPP, although its level of purity was not specified in this report, the same registered supplier of TPP as that used in this study states that its purity is >99%.

Methodology

Secondary activated sludge was obtained from a wastewater treatment plant in the Netherlands which had a predominantly domestic wastewater catchment. The proportion and nature of any industrial wastewater in the sewage was not stated. This activated sludge (400 mg dry weight/L) was preconditioned to reduce endogenous respiration rates by aeration for one week. Subsequently, the sludge was added to a nutrient medium and the test substance in bottles (see below). Ammonium chloride was omitted from the nutrient medium to prevent nitrification, this was considered a minor deviation which did not result in nitrogen limitation as shown by biodegradation of the reference compound. All other validity criteria were met.

Neither the diluted concentration of inoculum, nor the volume of filtrate used as inoculum was specified. The optimum volume to be used as inoculum for a given effluent should be determined through trial tests, so it is presumed the laboratory used prior experience to determine the appropriate volume within guideline criteria. Since the test substance is poorly soluble, silica gel ('Davisil grade 636', pore size 60A, 35-60 mesh particle size) was used as a carrier to accurately administer triphenyl phosphite. Although silica gel is not specifically referred to in the guideline, the use of auxiliary substances to deal with poorly soluble test substances are permitted provided that 'precautions are taken' - presumably to determined that the carrier is itself inert and does not influence degradation other that by acting as a surface on which to make the substance available. The ECHA Guidance on Information Requirements (R7b) also says that to counteract inoculum toxicity, testing may be performed by the introduction of carriers allowing the 'slow-release' of the test substance during the test period, although the amount of support used should be minimal.

The gel mix was prepared as a solid stock of 3.0 mg of the test substance added per g of silica gel in a 50-mL serum flask. Only part of the top layer of the silica gel was brought into contact with the test substance. The serum flask was closed and the content was mixed vigorously. Subsequently 0.2 g of silica gel with the test substance was added to the 0.3 L test bottles. The resulting concentration of the test substance in the bottles was 2.0 mg/L. Bottles containing only inoculum; inoculum and silica gel; and reference compound sodium acetate (6.7 mg/L) and inoculum were also prepared as controls. Each of the prepared solutions was dispensed into the respective group of BOD bottles as follows such that all bottles were completely filled without air bubbles:

- 10 bottles containing only inoculum;
- 10 bottles containing inoculum, silica gel and test substance;
- 10 bottles containing inoculum, and silica gel; and
- 6 bottles containing sodium acetate, and inoculum.

Four fewer bottles containing the reference compound and inoculum were used than in the typical run described by the guideline. However, the number of bottles used for this procedure control is considered sufficient because of the consistent rapid biodegradation across the sodium acetate bottles reported below.

The zero time bottles were immediately analysed for dissolved oxygen and the remaining bottles were closed and incubated in the dark. Two duplicate bottles of all series were withdrawn for analyses of the dissolved oxygen concentration at day 7, 14, 21 and 28. Measurements and records were also made of pH and temperature. Endogenous respiration, theoretical oxygen demand (ThOD - calculated from the molecular formula of the test substance), biochemical oxygen demand (BOD) and biodegradation percentages were calculated.

Results

An endogenous respiration (oxygen depletion in the control (O_c)) of 0.9 mg/L at day 28 (Table 15) and the total mineralization of the reference compound, sodium acetate,

demonstrated the validity of the test. Sodium acetate was degraded by 83% of its theoretical oxygen demand after 14 days (Table 16 and Figure 1). The differences between the replicate values at day 28 were also less than 20%. Additionally there was little difference in the oxygen consumption between the two controls with and without silica gel, so the carrier itself did not affect respiration. The most important criterion was met by oxygen concentrations >0.5 mg/L in all bottles during the test period. This threshold ensures that the inoculum activity was not limited. The pH of the media ranged from 7.3 at the start of the test to 7.3 (both controls) and 7.1 (treatments) at day 28 and so was within the accepted range. Temperatures were also within the prescribed temperature range of 22 to 24 °C.

Inhibition of the endogenous respiration of the inoculum by the test substance at day 7 was not detected (Table 15). Therefore, no inhibition of the biodegradation due to the 'high' initial test substance concentration was expected.

The ThOD of triphenyl phosphite was 2.2 mg/mg and the ThOD of sodium acetate was 0.8 mg/mg. Triphenyl phosphite was biodegraded by 84% at day 28 (Table 16 and Figure 1). Over 60% biodegradation of TPP was achieved after approximately 6 days immediately following the attainment of 10% biodegradation (Figure 1). In order to be considered 'readily biodegradable', a test substance must achieve 60% biodegradation in a 10-d time window within the 28-d period of the test. The 10-d window begins when the degree of biodegradation has reached 10%. Hence, triphenyl phosphite was considered as being 'readily biodegradable' under the conditions of this test.

Table 15. Dissolved oxygen concentrations (mg/L) in Closed Bottle Test

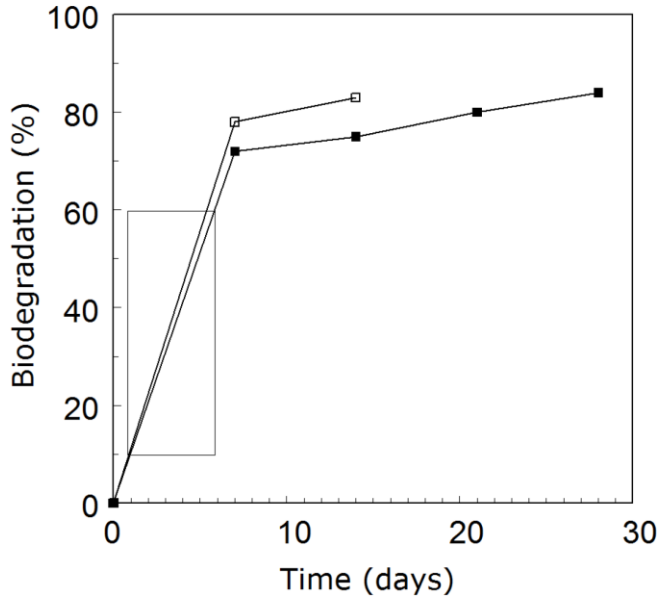
Time (days)	Oxygen concentration (mg/L)			
	Os_c	O_t	O_c	O_a
0	8.6	8.6	8.6	8.6
	8.6	8.6	8.6	8.6
Mean (M)	8.6	8.6	8.6	8.6
7	8.2	5.2	8.0	3.8
	8.2	5.0	8.1	3.9
Mean (M)	8.2	5.1	8.1	3.9
14	8.1	4.7	8.0	3.4
	8.0	4.9	8.0	3.5
Mean (M)	8.1	4.8	8.0	3.5
21	8.0	4.5	8.0	
	8.0	4.4	7.9	
Mean (M)	8.0	4.5	7.9	
28	7.8	4.0	7.7	
	7.8	4.2	7.7	
Mean (M)	7.8	4.1	7.7	

O_c Mineral salts medium with activated sludge
Os_c Mineral salts medium with activated sludge and silica gel
O_t Mineral salts medium with activated sludge and test substance (2.0 mg/L)
O_a Mineral salts medium with activated sludge and sodium acetate (6.7 mg/L)

Table 16. Oxygen consumption (mg/L) and percent biodegradation of TPP (BOD/ThOD) and sodium acetate (BOD/ThOD) in the Closed Bottle test. (Unpublished, 2015).

Time (days)	Oxygen consumption (mg/L)		Biodegradation (%)	
	Test substance	Acetate	Test substance	Acetate
0	0	0.0	0	0
7	3.1	4.2	70	78
14	3.3	4.5	75	83
21	3.5		80	
28	3.7		84	

Figure 1. Percentage of biodegradation of triphenyl phosphite (■) and sodium acetate (□) against time - determined in ready biodegradation Closed Bottle test. (Unpublished, 2015)



The box shows the time required to obtain 60% biodegradation of the test substance immediately following the attainment of 10% biodegradation.

eMSCA conclusions on ready biodegradation test (Unpublished, 2015)

This ready biodegradation study on TPP was conducted appropriately to OECD Guideline 301 D and in compliance with GLP. The adaptions to omit ammonium chloride from the nutrient medium and the use of silica gel as a carrier to administer the poorly soluble test substance can be accepted as they did not, in themselves, affect the respiration rate. The purity of the test substance was not included in the study report but is inferred as being high from the source specification. Whilst the diluted concentration of inoculum used was not specified, its satisfactory biological activity was confirmed in the results. The test is considered valid due to an endogenous respiration of 0.9 mg/L and by the degradation of the reference compound, sodium acetate, by 83% of its theoretical oxygen demand after 14 days. Oxygen concentrations were also >0.5 mg/L in all bottles during the test period. It is proposed, and the eMSCA agrees, that this study has a Klimisch reliability score of 1 (reliable without restriction).

Overall, the results showed that triphenyl phosphite was biodegraded by 84% at day 28 and over 60% biodegradation was achieved in a period of 6 days immediately following the attainment of 10% biodegradation. Hence, triphenyl phosphite can be considered as being 'readily biodegradable' under the conditions of this study.

7.7.2.1.2.1. Overall summary and conclusions regarding ready biodegradation

The original experimental screening study (Unpublished, 2003) suffered from a number of methodological and reporting issues, mainly caused by the very low water solubility and lack of bioavailability of TPP to the inoculum. A more recent and reliable study (Unpublished, 2015), also to OECD TG 301 D, used an inert silica gel carrier for the TPP and this showed a contrasting very high level of biodegradation with 84% degraded by day 28, over 60% of which was achieved within the 10-day time window.

The update of OECD GD 23 (Guidance document on Aqueous Phase Aquatic Toxicity Testing of Difficult Test Chemicals; Revised August 2017 currently unpublished) contains details in Section 7 and Annex 6 that give an overview of loading principles and techniques in the application of passive dosing. The main principles are to establish and maintain a freely dissolved concentration of a poorly soluble test substances in aquatic testing. A biocompatible polymer is first loaded with test chemical and then included in the test system where it acts as a partitioning donor that controls exposure concentrations throughout test duration. This concept has been applied to both individual substances and UVCBs. Overall the use of silica polymer as a passive dosing technique can be considered acceptable in both the hydrolysis and ready biodegradation studies.

Hence, triphenyl phosphite was considered to be 'readily biodegradable' under the conditions of this study.

7.7.2.1.3. Simulation tests (water and sediments)

Data waiving

Reason: Registrant(s) considers studies to be scientifically unjustified.

Justification by Registrant: *'TPP is subject to rapid hydrolysis in water (abiotic degradation) but it is also very poorly soluble in water. A screening test for biodegradation of TPP in water indicates the substance to be readily biodegradable, additional biological degradation testing in sediment is not needed. Hydrolysis products are separately registered and are considered readily biodegradable'*.

In ECHA's Decision dated 2/10/2015, the following information request was made:

- Aerobic Mineralisation in Surface Water - Simulation Biodegradation Test (test method EU C.25/OECD 309) with natural freshwater and amended with sediment, including both the kinetic transformation and the pathway of transformation at 12 °C. The test with suspended sediment shall be performed using sediment characterised by high organic carbon content (2.57.S%) and a fine texture. The test substance concentration should be in the range of the water solubility of the substance, preferably 2-20 µg/L.

In response to this request for an OECD TG 309 surface water simulation biodegradation test, the lead Registrant has made the following case:

'At the time of this request for this test, the existing data indicated that TPP was not biodegradable and the available hydrolysis data had not been generated under sufficiently realistic conditions (i.e. without high levels of co-solvent) to allow any definitive conclusions regarding hydrolysis under relevant environmental situations. Subsequently, another ready biodegradation test (301 D) was conducted in which TPP was dosed in a manner recommended within the OECD 301 guideline (Annex III) for improving the bioavailability of poorly soluble test materials being tested well above their solubility limit. In this second test, TPP was rapidly and extensively biodegraded and met all the criteria to be considered "ready biodegradable". In addition, an OECD 111 hydrolysis study without co-solvent was conducted that demonstrated that TPP undergoes rapid hydrolysis directly to phenol and phosphorous acid at pHs ranging from 4 to 9. Importantly, it showed that TPP has a half-

life less than 15 hrs at pH 7 and 12° C, which is particularly relevant for waste waters. Given these new data, the OECD 309 test was no longer deemed necessary'.

Consideration of justification by the eMSCA: The justification for not submitting a water or sediment simulation test on TPP is considered reasonable based on the most recently submitted hydrolysis (Unpublished, 2017c) and ready biodegradation tests (Unpublished, 2015) evaluated above in Sections 7.7.1.1 (iii) and 7.7.2.1.2 (ii) respectively. TPP is of very low water solubility but the new hydrolysis and biodegradation studies indicate rapid degradation of any TPP that is or becomes available for hydrolytic or biotic reactions. Information from other sources, e.g. the EU Risk Assessment Report for phenol (European Chemicals Bureau, 2006) concludes that this main hydrolysis product of TPP is also readily biodegradable. The other potential degradant is inorganic phosphorous acid.

The high estimated log Kow of TPP (6.62) indicates a potential for TPP to partition and adsorb to sediment as well as dissolved organic matter and particulates (see distribution modelling below). However, it appears that any desorbed and bioavailable TPP is rapidly abiotically and biotically degraded, and so additional aqueous and simulation testing is not considered to be warranted.

7.7.2.1.4. Biodegradation in soil

Data waiving

Reason: Registrant considers study to be scientifically unjustified.

Justification by Registrant: **'***TPP is subject to rapid hydrolysis in water (abiotic degradation) and is also very poorly soluble in water. A screening test for biodegradation of TPP in water indicates the substance to be readily biodegradable, additional biological degradation testing in soil is not needed. Hydrolysis products are separately registered and are considered readily biodegradable*'.

Consideration of justification by eMSCA: The justification for not submitting a soil simulation test on TPP is considered reasonable based on the most recently submitted hydrolysis (Unpublished, 2017c) and ready biodegradation tests (Unpublished, 2015) evaluated above in Sections 7.7.1.1 (iii) and 7.7.2.1.2 (ii) respectively. TPP is of very low water solubility but the new hydrolysis and biodegradation studies indicate rapid degradation of any TPP that is or becomes available for hydrolytic or biotic reactions. As mentioned in Section 7.7.2.1.3, the organic transformation product, phenol, is also readily biodegradable.

The high estimated Log Kow of TPP (6.62) indicates a potential for TPP to partition and adsorb to soil particles and organic matter (see distribution modelling below). However, to reach the soil compartment any TPP emitted in waste streams from industrial production or usage sites would first travel through waste water treatment plants (WWTP) and any desorbed and bioavailable TPP would be rapidly abiotically and biotically degraded. It is possible that some TPP still adsorbed to sludge in WWTP could subsequently be returned to soil, however the levels of biodegradation seen in the unpublished biodegradation study (2015) - 84% at day 28 and >60% within 6 days following attainment of 10% degradation, indicate that amounts transferred to soil should be extremely low.

Any direct exposure of soil from use in coatings, adhesives and lubricants in more open systems is also expected to be very low and once released to soil and soil water it should also undergo rapid abiotic and biotic degradation. The exposure modelling and risk calculations in Sections 7.12 and 7.13 instead focus on the main degradation product, phenol. Overall therefore, additional soil simulation testing on TPP itself is not considered to be warranted.

7.7.3. Environmental distribution

7.7.3.1. Adsorption/desorption

Data waiving

Reason: Registrant considers study to be scientifically unjustified and technically not feasible.

Justification by Registrant: TPP is subject to rapid hydrolysis in water (abiotic degradation) and therefore is not anticipated to be in the environment for an extended period to warrant adsorption/desorption studies.

Consideration of justification by eMSCA: Based on the most recently submitted hydrolysis (Unpublished, 2017c) and ready biodegradation tests (Unpublished, 2015) evaluated above in Sections 7.7.1.1 (iii) and 7.7.2.1.2 (ii) respectively, the case regarding rapid degradation of TPP appears to be reasonable once the substance is solibilised and available for biotic and abiotic degradation. Information from other sources, e.g. ECB Phenol Risk Assessment Report (2006), indicates that the hydrolysis products are themselves readily biodegradable or inorganic and due to a low predicted Log Koc are unlikely to partition to or concentrate in soil. Overall the eMSCA agrees that further tests specifically on adsorption/desorption of TPP are not required in this substance evaluation.

7.7.3.2. Volatilisation

TPP has a very low vapour pressure (0.069 Pa at 25°C from Section 7.4) and is not expected to partition to the atmosphere to any significant extent. No other information has been submitted and it is not considered necessary for this evaluation.

7.7.3.3. Distribution modelling

Fugacity Level III QSAR modelling using EPIWIN v 3.10 has been included in the lead Registrant's dossier. This is itself largely based on an estimated Log Kow for TPP of 6.22 and so is considered as Klimisch 2 (reliable with restrictions). Based on these assumptions alone and equal emissions to all three compartments, the majority of TPP would partition to the soil and sediment as reported in the following table:

Table 17. Fugacity Level III QSAR results for TPP based on EPIWIN v.3.10 modelling

	Mass amount (%)	Half-life (hrs)*	Emissions (kg/hr)
Air	0.474	23.7	1000
Water	4.44	900	1000
Soil	30.3	900	1000
Sediment	64.8	3.6×10^3	0

* These half-lives have not been updated since the latest degradation studies were submitted

Similar results were obtained based on just emissions to water. With emissions to just air or soil, the majority of the releases partition to the soil compartment. These results are not unexpected based on the high estimated Kow value which drives the model. These distributions do not, however, consider the rapid hydrolysis and biodegradation of TPP, which is envisaged to be an important factor influencing its environmental distribution. The half-lives used for TPP are set at high default levels.

Information from other sources, e.g. ECB RAR on phenol (2006), and registration dossiers for phosphorous acid, indicates that the degradation products of TPP are themselves readily

biodegradable or inorganic and, due to a low predicted Log Koc (82.8 L/kg for phenol), are unlikely to partition to and concentrate in sediment or soil. Phosphorous acid is an inorganic diprotic acid (readily ionizes two protons) with pKa values of 1.3 and 6.6, so it will be ionic at environmental pHs. TPP has a very low vapour pressure (0.069 Pa at 25 °C from Section 7.4) and is not expected to partition to the atmosphere to any significant extent.

7.7.4. Bioaccumulation

The Log K_{ow} for TPP referenced in Section 7.4 is 6.62, although this is only estimated rather than measured and should be viewed with some caution. A value this high would normally indicate a potential for aquatic bioaccumulation as it exceeds the REACH screening Log Kow value of ≥4.5. According to the lead Registrant, no evidence of bioaccumulation of TPP has been found in literature searches and an experimental bioconcentration factor (BCF) cannot be obtained for TPP because of its low water solubility as well as rapid hydrolysis. An experimental fish bioaccumulation study using OECD TG 305 (water or dietary exposure) has therefore been waived as not technically feasible.

Bioconcentration factors (BCF) for TPP were estimated by calculation using the US EPA BCFBAF v3.00 model. The Registrant considered this an accepted model for calculation of bioaccumulation potential and considers the modelling studies to be 'reliable with restrictions' (Klimisch 2). Since the Log Kow was itself estimated, this should be taken in to account when considering the overall reliability of the model. The equation initially used to make the BCF estimate according to BCFBAF v3.00 was: Log BCF = 0.6598 log Kow - 0.333 + correction. No correction factor was considered applicable for TPP. Various other transformations were then applied and a number of resulting BCF estimates for TPP have been included in the lead Registrant's dossier as follows:

- Log BCF from regression-based method = 4.038 (BCF = 10910 L/kg wet-wt)
- Log Biotransformation half-life (Log HL) = 0.6061 days (HL = 4.038 days)
- Log BCF Arnot-Gobas method (upper trophic) = 2.936 (BCF = 862.2)
- Log BAF Arnot-Gobas method (upper trophic) = 3.532 (BAF = 3403)

BCF values vary from 862.2 L/kg based on Arnot-Gobas method to 10,910 L/kg based on the BCFBAF v3.00 regression-based QSAR method. An unpublished 2012 UK Environment Agency Review of the BCFBAF model within EPIWEBv4 indicated uncertainty associated with predictions of BCFs and BMFs according to the Arnot-Gobas method and showed these are not necessarily similar to a BCF from a laboratory test based on the dissolved concentration in water. The predictions at low to moderate log Kow values are probably more reliable than the predictions at very high Log Kow, owing to uncertainties in the underlying BCF database for high Log Kow substances. It is proposed by the Registrants that the BCF regression equation is used in preference to the Arnot-Gobas method for substances with Log Kow values up to around 7-8 (for TPP it is estimated as 6.62). This is because there are fewer assumptions built into the regression equation compared with the Arnot-Gobas method. Above Log Kow values of 7-8, the underlying BCF database is uncertain and so the uncertainty in the predictions using either method is higher than for the substances with lower Log Kow values. Again it is proposed that the estimates from the regression equation are used over estimates from the Arnot-Gobas method.

Overall however, there is a broad range of results from these methods and none of them fully consider either hydrolysis or biotransformation of the substance, both of which are expected to be rapid (as shown in the studies at Sections 7.7.1.1 (iii) and 7.7.2.1.1.2 (ii)). Give this uncertainty it is not proposed to rely on this modelling information for TPP, reliable BCF values for TPP are therefore difficult to obtain and due to its rapid hydrolysis as well as biodegradation, the overall potential for bioaccumulation of TPP is expected to be low. It may be more relevant in any case, to focus on the hydrolysis products, phenol and phosphorous acid.

The experimental Log Kow of phenol (the primary hydrolysis product) is 1.47 and its BCF is 17.5 L/Kg (European Chemicals Bureau, 2006)) and phosphorous acid, which is inorganic, has an uncorroborated BCF of 2.68 L/kg wet-wt (BCFBAF 3.01, source: REACH public registration dossier). This information supports the conclusion that neither TPP nor its hydrolysis products are expected to bioaccumulate and they do not meet the criteria for B or vB (see Section 7.11) or pose a bioaccumulation risk in aquatic or terrestrial systems or from secondary poisoning.

7.7. Environmental hazard assessment

A number of unpublished studies were included in the registration dossier (as robust study summaries), and have been used during the evaluation. Full references are not given in this report.

7.8.1. Aquatic compartment (including sediment)

All of the short- and long-term aquatic ecotoxicity endpoints for TPP (i.e. on fish, aquatic invertebrates. algae and aquatic plants, sediment-dwelling organisms) have been waived in the lead Registrant's dossier. The justification for data waiving is essentially the same for each aquatic group, i.e. the substance is very poorly water soluble and what does dissolve is subject to rapid hydrolysis or biodegradation (as described in the Environmental Fate Section 7.7). Conducting experimental toxicity studies was therefore considered technically not feasible, even taking in to account methods in OECD GD No. 23 - the 'Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures' (OECD 2000). After conducting a literature search, the lead Registrant has stated that no valid experimental ecotoxicological endpoints for TPP itself could be found.

The lead Registrant concluded that, since direct measurements of the ecotoxicity of the parent substance would be extremely difficult, the testing program should focus on quantifying the combined toxicity of hydrolysis products of TPP. Therefore, as an attachment to their dossier the Registrants have submitted an assessment of the aquatic toxicity of 'aged TPP' based on the proportions formed and toxicity of its hydrolysis products (phenol and phosphorous acid) and assuming additive toxicity; this is described below:

According to the reported methodology, a detailed literature search was conducted to assess the available database of information relating to the acute toxicity of phenol and phosphorous acid to fish, daphnids and algae. Where sufficient data were unavailable in the scientific literature, ECOSAR (US EPA, 2001) was used to model their potential ecotoxicity - this applied to the endpoints for phosphorous acid. Measured and calculated acute/short-term aquatic toxicity values (EC_{50}) for the individual primary hydrolysis products of TPP were therefore identified and a summary of these is provided in their report (and in the table below). Using these data, quantitative predictions were made of the acute/short-term ecotoxicity values (solution toxicity values) based on the sum of the ratios of the maximum theoretical concentration of the individual hydrolysis products in solution (at their limit of solubility). This was based on the following stoichiometry:

Under hydrolysis, one mole TPP (molar weight (mw) = 310.29 g/mole) yields three moles phenol (mw = 94.11 g/mole) and one mole phosphorous acid (mw = 82.00 g/mole);

The range of water solubility values for TPP from Section 7.4 is 0.002 to 0.3 mg/L. Taking as a worst case the maximum limit of 0.3 mg/L, TPP would hydrolyse to 2.9×10^{-6} moles/L phenol and 9.7×10^{-7} moles/L phosphorous acid. These molar concentrations equate to mass concentrations of 0.27 mg phenol/L and 0.079 mg phosphorous acid/L respectively.

This modelling results in the following 'solution toxicity values' for the mixture of hydrolysis products of TPP at its proposed maximum aqueous solubility limit:

Table 18. Lead Registrant's calculated aquatic toxicity of 'aged TPP' based on the proportions and toxicity of its hydrolysis products.

Aquatic toxicity values	Phenol EC_{50} (mg/L)[1]	Calculated phenol concentration (mg/L)	Phosphorus acid EC_{50} (mg/L)[2]	Calculated phosphorus acid concentration (mg/L)	Calculated solution toxicity values
Fish	8.9	0.27	383	0.079	0.031
Daphnia	10.1	0.27	387	0.079	0.027
Algae	144.2	0.27	230	0.079	0.0022

[1] Source ECB 2006 Phenol Risk Assessment Report
[2] Calculated value (using ECOSAR; US EPA, 2001)

Using this method, the representative ecotoxicity values (EC_{50}) for the mixed 'aged TPP' solution were therefore determined to be: 0.0022, 0.027, and 0.031 for algae, daphnids, and fish, respectively. There are no units for these values but a derived solution toxicity value of 1.0 is considered equivalent to an acute EC_{50} value for the 'aged' solution (i.e., it would predict 50% acute mortality/growth inhibition in the test species based on the theoretical concentrations). The further below a value is from 1, the lower the inferred ecotoxicity hazard. Correspondingly, as a value approaches or exceeds 1.0, the greater the inferred ecotoxicity hazard. On this basis, these calculations, with values well below 1, indicate that the mixture of hydrolysis products arising from an initial saturated solution of TPP, would essentially be not toxic to aquatic organisms.

The basis for this approach appears theoretically feasible, however it relies on a number of assumptions:

- Results have been estimated based on the maximum water solubility of TPP, however this is taken from a limited range of estimated and literature values. Solubility of TPP does appear to be very low however, and it might be possible to consider calculations or experimentation based on loading rates (as done for metals).

- Whilst the toxicity endpoints for phenol have been evaluated in the ECB 2006 Phenol Risk Assessment Report (prepared by Germany) and are considered reliable, the data for phosphorous acid are calculated using the US EPA's ECOSAR model. Whilst ECOSAR is generally considered to be a suitable model, included in the OECD QSAR Toolbox, the reliability and applicability of the individual QSAR estimates for phosphorous acid have not been well demonstrated or documented, e.g. according to ECHA's QSAR prediction reporting format (QPRF). As a simple acid, any effects may just be as a consequence of pH change. Since production of these calculations, other experimental data have been found in unevaluated public EU Registration dossiers for phosphorous acid (as phosphonic acid, EC no. 237-066-7). The data ownership and reliability of these data is unclear, so they have not been considered in detail here. It would be worth the Registrants for TPP seeking their use, checking their reliability and comparing them against their own estimates. Phosphonic and phosphorous acid have the same chemical formula (H_3PO_3) the difference is that phosphonic acid is a shelf-stable compound while phosphorous acid is extremely short-lived and immediately tautomerises to phosphonic acid. An initial consulation of the public data indicates acute aquatic EC_{50} values for fish of ≥ 100 mg/L, for *Daphnia* of ≥ 1000 mg/L and for algae of 153 mg/L. So, the latter value is potentially lower than that estimated for algae, although it is still a high and not likely to lead to any hazard/risk concerns.

- How these theoretical solution toxicity values for 'aged TPP', would be used is also an important consideration - they might have some use for hazard assessment, but maybe less useful for risk assessment purposes. The Registrant(s) has not actually used them for PNEC derivation in Sections 7.8.3, preferring instead to conduct the exposure and risk assessments based on phenol alone.

- These ecotoxicity estimates only cover acute/short-term aquatic toxicity. TPP is registered as a 100-1000 tonnes per annum substance (agglomerated total tonnage for all uses) so falls within the REACH Annex IX. According to the Information Requirements (9.1.5-6) at this and lower tonnage bands, the Annexes propose that long-term aquatic toxicity to *Daphnia* and fish shall be considered if the substance is 'poorly water soluble'. The lead Registrant's waiver regarding the lack of long-term testing are that (as with acute/short term tests) such testing is technically not feasible since the substance is 'very poorly soluble' and what does dissolve is subject to rapid hydrolysis. Their CSA also does not indicate a need for further testing and it is assumed that any solubilised TPP would rapidly degrade and so not pose a chronic hazard or risk.
  No chronic hazard assessment for the degradation products, phenol and phosphorous acid is included; chronic endpoints are however available for phenol in the ECB 2006 RAR and for completeness the mixed 'aged TPP' solution calculations could have included these. However, the ECB 2006 RAR does not indicate any unacceptable acute or chronic environmental hazard or risk from phenol. Due to its much lower overall tonnage, any limited contribution from degradation of TPP is unlikely to substantively increase this.

Overall, the eMSCA agrees with the lead Registrant's justifications for not conducting aquatic ecotoxicity tests on TPP itself, owing to its low solubility and demonstrated rapid hydrolysis and biodegradation. Although flow-through tests (for fish at least) and other methods suggested by the OECD 'Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures' (OECD GD No. 23, 2000) could be tried to dissolve, disperse or retain TPP in aqueous solution, or to test the aged solution instead - how environmentally realistic or representative any such results would be is questionable. The lead Registrant states that such methods have been considered but were not technically feasible and no reliable endpoints for TPP have been found in a literature search. Despite some reservations, their proposed strategy based on the toxicity and proportions of TPP hydrolysis products, may therefore be an appropriate method for aquatic hazard determination.

7.8.2. Terrestrial compartment

As discussed above in Section 7.8.1., no valid experimental endpoints for TPP could be found in a literature search by the lead Registrant, including in the terrestrial compartment. The Registrant has not undertaken any direct experimental ecotoxicity tests on terrestrial organisms using TPP. They have waived all terrestrial test requirements based on the justification that they do not need to be conducted because direct and indirect exposure of the soil compartment is unlikely. Also because TPP is subject to rapid hydrolysis and biotic degradation, they do not expect the terrestrial compartment to be important exposure route for TPP risk assessment.

Low water solubility and rapid hydrolysis of TPP do not themselves prevent testing in soil and the high estimated Log Kow of TPP indicates that it might preferentially adsorb to soil (see distribution modelling at Section 7.7.3). However, to pose a hazard or risk in soil, TPP would first need to reach the terrestrial compartment. The usual indirect route of such exposure considered for industrial substances is via amendment of soil with contaminated sewage sludge. As demonstrated by the environmental fate studies considered in Section 7.7, rapid hydrolysis of TPP is expected in the aquatic routes (washings and waste streams) potentially leading to contamination of waste water treatment plants (WWTP). Once in the WWTP, rapid biodegradation of TPP is also envisaged, as demonstrated by its ready biodegradation (84% degraded by day 28, over 60% achieved within the 10-day time window - ref. Section 7.7.2.1.2). This indicates that indirect exposure of soil to parent TPP is unlikely.

The lead Registrant also considers that there is unlikely to be direct soil contamination resulting from the proposed professional and consumer uses of TPP, however rapid hydrolysis and biotic degradation of TPP are also expected to occur following any direct

application to moist soil. As such, the eMSCA also does not consider terrestrial exposure to be significant for parent TPP and the individual data points for terrestrial organisms (including higher terrestrial organisms like birds) can therefore been waived.

The hydrolysis product (phenol) has previously been assessed in relation to its terrestrial hazard and risk in the ECB 2006 Phenol Risk Assessment Report and was not determined to pose a concern. Any additional contribution from the breakdown of TPP is considered to be minimal. The other inorganic degradation product, phosphorous acid will be ionic at environmental pHs and will likely react with soil particles, other chemicals and organic matter and not substantively increase natural background soil phosphorous/phosphate concentrations.

Overall the eMSCA does not consider that further studies on the effects of TPP on soil or other terrestrial organisms are warranted.

7.8.3. Microbiological activity in sewage treatment systems

Other than in the ready biodegradation tests using activated sewage sludge (evaluated in Section 7.7.2.1) no other experimental studies on the effects of TPP on micro-organisms present in sewage treatment systems could be found by the lead Registrant. The Registrant considers that there is unlikely to be direct contamination of sewage treatment plants from the proposed uses of TPP, because of its rapid hydrolysis. As such the Registrant has therefore waived the data point for aquatic micro-organisms. It is also noted that the OECD 301D closed bottle biodegradation studies considered in Section 7.7.2.1 indicate that the TPP did not inhibit microbial activity at the concentrations tested (2-10 mg/L, so greater than the stated water solubility) and it was subsequently readily and rapidly degraded when made available for biotic reactions.

The hydrolysis product (phenol) has been considered in relation to its hazard and risk to microorganisms in WWTP in the ECB 2006 Risk Assessment Report and was not determined to pose a concern based on site specific data and realistic effluent concentrations. Relatively, any additional contribution of phenol from the breakdown of TPP is considered to be minimal and ionic inorganic phosphorous acid is not considered to pose a concern to WWTP given minimal exposure.

Overall the eMSCA does not consider that further studies on the effects of TPP on micro-organisms present in sewage treatment systems are warranted.

7.8.4. PNEC derivation and other hazard conclusions

The lead Registrant has presented a case stating that it is not possible to undertake ecotoxicity tests on TPP due to its very low solubility and rapid hydrolysis. This is accepted by the eMSCA (see Section 7.8) and so the environmental PNECs and subsequent risk assessment were therefore based on phenol, it's primary hydrolysis product. Upon hydrolysis, one mole of TPP produces three moles of phenol. Established PNECs for phenol were derived from the European Chemicals Bureau (ECB) 2006 Risk Assessment Report prepared by Germany. The PNECs for phenol are summarised in the table below. Although the lead Registrant has not provided any quantification/ comparison against, e.g. environmental background or other anthropogenic levels of phenol, any additional contribution of phenol from the breakdown of TPP is expected to be relatively minimal.

Phosphorous acid is also a hydrolysis product of TPP; one mole of TPP produces one mole of phosphorous acid. Information is lacking on phosphorous acid but ECOSAR-calculated endpoints and those from the public registration dossier indicate it to be of low short term aquatic ecotoxicity. This acid is expected to be ionic in solution at relevant environmental pH and will likely react or bind with other particles, chemicals and organic matter in environmental compartments forming phosphorous compounds which are unlikely to exceed natural background levels. Since the element phosphorous is an essential plant

nutrient and phosphorous acid and its salts were consider by the Registrant to have relatively low plant, animal and human toxicity, it is proposed that at the levels produced phosphorous acid will not have any significant impact on the environmental assessment of TPP. As such, the environmental assessment has focused just on phenol. The eMSCA agrees with this proposal.

Table 19: Environmental PNECs determined for degradation product phenol (not determined for TPP itself)

PNEC DERIVATION AND OTHER HAZARD CONCLUSIONS		
Hazard assessment conclusion for the environment compartment	**Hazard conclusion**	**Remarks/Justification**
Freshwater	7.7 µg/L (0.0077 mg/L)	Established PNEC for the primary hydrolysis product, phenol (ECB, 2006), this has been checked by the eMSCA and is correct.
Sediment	115.6 mg/kg dry weight	PNEC for the primary hydrolysis product, phenol. This does not appear in ECB (2006) for phenol since...[quote] '*there is nothing indicating that phenol accumulates in sediment*' - therefore it is unclear where this figure is from (it may be equilibrium partitioning value derived from the freshwater PNEC). However the RAR does conclude there is low risk via exposure of sediment to phenol.
Sewage treatment plant	2.1 mg/L	Established PNEC for the primary hydrolysis product, phenol (ECB, 2006), confirmed by eMSCA.
Soil	136 µg/kg dry weight (0.136 mg/kg)	Established PNEC for the principle hydrolysis product, phenol (ECB, 2006), confirmed by eMSCA.
Air		Not considered
Secondary poisoning		Given its rapid abiotic and biotic environmental degradation, TPP is expected to have a low bioaccumulation potential. Phenol also has a low bioaccumulation potential and is not considered a risk *via* secondary poisoning (ECB, 2006).

Overall, use of the PNECs previously determined for phenol are considered to be a potentially useful surrogate for any that might be determined for TPP (although this appears unlikely given its chemical nature). The mixture toxicity calculation included in Section 7.8.1 has not been used to also derive PNECs for 'aged TPP'.

7.8.5. Conclusions for environmental classification and labelling

The existing harmonised aquatic hazard classification of TPP in Annex VI of the CLP Regulation is Aquatic Acute 1 (H400) and Aquatic Chronic 1 (H410) - see Section 4.1.1. This classification was translated across from a classification under the Dangerous

Substances Directive of R50/53. The basis for this classification is unclear as the ECB Classification Technical Meeting minutes are no longer available.

Whilst the lead Registrant(s) apply this classification they believe it to be inappropriate - quote from dossier: *'There is no clear basis for this classification and due to the rapid hydrolysis of TPP it is simply not possible to test its aquatic toxicity reliably. The hydrolysis products for TPP, phenol and phosphorous acid, are not classified as dangerous to the environment, further supporting the conclusion that TPP will not be toxic to aquatic organisms'*.

In the absence of data to the contrary the eMSCA does not propose to revisit this classification. However, as the recommendation of this evaluation is a that a CLH proposal is taken forward with respect to additional human health hazard endpoints (see Sections 7.12.1 and Part A 4.4.1) this would be an opportunity for the environmental classification to be reconsidered. In this case the Registrant should reconsider what data they wish to use to support any such re-classification and it may be worth attempting to conduct some supporting ecotoxicity tests, or refining the theoretical 'aged TPP' solution toxicity calculations (using the new degradation information and available data on phosphorous acid for example).

7.8. Human Health hazard assessment

The initial focus of the human health evaluation was the effect of TPP on reproductive, behavioural and neurotoxicity end-points and its potential for skin sensitisation, as these were the identified grounds for concern. The substance's endocrine disrupting properties were also evaluated.

As one of the initial aims of the evaluation was to check that exposure to TPP is adequately controlled, DNELs were derived based on the information in the registration dossier to take forward for risk characterisation.

Additionally a screen of all the available information was conducted to identify any additional potential concerns. From this screen, concerns regarding the robustness of the data package, particularly regarding mutagenicity, were identified.

Following the initial evaluation, a decision was issued requesting that the registrants submit an *in vitro* micronucleus study and a bacterial reverse mutation test. These studies were evaluated in full.

A number of unpublished studies were included in the registration dossier (as robust study summaries), and have been used during the evaluation. Full references are not given in this report.

7.8.1. Toxicokinetics

Summary and discussion of toxicokinetics

No toxicokinetic studies are available for TPP. The following summary is based on that provided in the registration dossier.

The metabolism of TPP has been described as involving step-wise hydrolysis of the parent phosphite with release of phenol, or oxidation of the parent compound to triphenyl phosphate with subsequent step-wise hydrolysis to release phenol (Abou-Dania, 1992). This is supported by the hydrolysis data in the dossier, which shows rapid hydrolysis from TPP to phenol with little accumulation of intermediate products. Complete metabolism would result in the release of three molecules of phenol, and phosphoric acid. The hydrolysis rate of TPP is pH-dependent.

While there are no specific toxicokinetic studies of TPP, toxicology testing appears to indicate that it is readily absorbed via the oral route. Due to its rapid hydrolysis in water, with a half-life of 0.5 hours at neutral pH, it may be appropriate to consider the toxicokinetics of phenol for oral and inhalation routes since there would be a high likelihood of hydrolysis via these routes. The Phenol RAR (ECB 2006) concludes 100% absorption via the oral and inhalation routes and rapid elimination with low potential for bioaccumulation.

There are currently no specific studies on the dermal absorption potential of TPP. However, there are multiple sources of guidance that indicate for substances with a log Kow (Pow) above 5 or 6 that the potential for dermal absorption will be minimal/negligible, including:

Guidance on Information Requirements and Chemical Safety Assessment. Chapter R.7c Table R.7.12-3 (ECHA 2017): [For Log K_{ow}] "*above 6, the rate of transfer between the stratum corneum and the epidermis will be slow and will limit absorption across the skin. Uptake into the stratum corneum itself may be slow*".

ECOTOC TRA manual (Technical Report No. 93, p. 31 (ECETOC (2004)):"*Substances that are unlikely to constitute any dermal risk through absorption due to their physico-chemical properties are not considered. Such cases are when the substance has either high hydrophobicity (log Kow > 5), high hydrophilicity (log Kow < -1) or a high molecular weight (>1,000)*"

TPP has an estimated Log Kow of 6.6, and therefore it seems appropriate to consider an absorption rate of less than 100%. EC guidance recommends a dermal absorption rate of 10% for substances with high Kow's and molecular weights (EC Health & Consumer Protection DG 2004), though TPP's molecular weight is somewhat below the criterion in this guidance document. Hydrolysis product (phenol) information was considered for the oral and inhalation routes, though it is not clear that the potential for hydrolysis is as great via the dermal route as it would be for the oral and inhalation routes, especially since TPP is a skin irritant and skin sensitiser and therefore resident time on the skin is likely to be short. Phenol's dermal absorption rate is 80% (ECB 2006). Based on the various considerations, the registrants have used an absorption rate of 50% in their assessments. They believe this to be sufficiently conservative given the potential for hydrolysis, though also recognising the likelihood of limited dermal uptake based on TPP's high Kow.

The eMSCA notes that the registrants have indicated that they plan to conduct dermal absorption testing in order to refine this value.

7.8.2. Acute toxicity and Corrosion/Irritation

This information is not relevant to the evalutation but a brief summary has been included for completeness.

Summary and discussion of acute toxicity

The acute toxicity of TPP has been investigated by the oral, inhalation and dermal routes.

The oral LD_{50} of 1590 mg/kg indicates that a classification of Acute Tox. 4 – H302 is appropriate; this has been applied by the registrants in their registration dossiers. The eMSCA agrees with this classification.

The results of the inhalation (LC_{50} > 6.7 mg/L) and dermal (LD_{50} > 2000 mg/kg) routes of exposure indicate that TPP does not meet the criteria for classification of these end-points.

Irritation

This information is not relevant to the evaluation but a brief summary has been included for completeness.

Summary and discussion of irritation

The observations of skin and eye irritation in the tests available in the registration dossier are consistent with TPP's harmonised classifications for irritation (Skin Irrit. 2 – H315) and eye damage (Eye Irrit. 2 – H319). No information on respiratory tract irritation is available.

Corrosivity

TPP did not demonstrate corrosivity in skin and eye irritation studies.

7.8.3. Sensitisation

Skin

Sensitisation was one of the identified grounds for concern. The result of a recent study on skin sensitisation is summarised in the following table.

Table 20. Studies on skin sensitisation

Method	Results	Remarks	Reference
Mouse Local lymph node assay OECD Guideline 429 (Skin Sensitisation: Local Lymph Node Assay)	Sensitising Stimulation index: 2.5% = 5.16 5% = 7.79 10% = 7.84 EC3 value = 1.4%	1 (reliable without restriction) key study **Test material (EC name): triphenyl phosphite**	Unpublished report (2010)
Guinea pig (20/test group, 10 controls) Maximisation test OECD guideline 406	Sensitising = 90 / 95% positive 24/48 hours after challenge; 0 in control group Intra-dermal induction concentration = 5% Topical induction concentration = 20% Topical challenge concentration = 10% (occlusive)	1 (reliable without restriction) **Test material (EC name): triphenyl phosphite**	Unpublished report (2010)

Respiratory system

No information available.

Summary and discussion of sensitisation

A recent local lymph node assay indicates that TPP has the potential to induce skin sensitisation (stimulation index > 3), with an EC3 value of 1.4%. In accordance with the second ATP to CLP (Regulation 286/2011), TPP therefore meets the criteria for classification as Skin Sens. 1A – H317.

A guinea-pig maximisation test was also available, in which TPP tested positive. From the induction concentrations used, the Registrants concluded that TPP met the criteria for Skin Sens. 1B in this study. Nevertheless, since the LLNA is more appropriate than the guinea-pig tests for the determination of skin-sensitisation potency, the eMSCA concludes that the data from this study supports that of the LLNA but does not over-ride the finding in the latter that TPP is a strong skin sensitiser. Additional information supporting the conclusion that TPP is a skin sensitiser comes from two publications that report cases of allergic contact dermatitis in humans after the wearing of TPP-containing PVC gloves (Suuronen *et al.*, 2012; Vandevenne *et al.*, 2013)

TPP does not currently have a harmonised classification for skin sensitisation. The registrants have specified in their registration dossiers that they apply the self-classification Skin Sens. 1 – H317.

No further information is required to clarify the concern. However, the eMCSA recommends that a CLH proposal is taken forward to classify TPP as Skin Sens 1A.

7.8.4. Repeated dose toxicity

The repeated-dose toxicity of TPP has been investigated in a combined repeated-dose toxicity study with the reproduction / developmental toxicity screening test (OECD 422).

Several grounds for concern were identified from this study: the reproductive, behavioural and neurotoxicity endpoints, and possibly endocrine-disrupting properties. A full evaluation of this study was thus conducted to inform on these concerns, and additionally repeated-dose toxicity was evaluated. To enable this, the lead registrant provided the full study report.

The findings of the study relevant to repeated-dose toxicity are described in this section. The findings relevant to reproductive toxicity are described in depth in section 7.9.7, and to endocrine disruption in section 7.10.1.

Non-human information

Repeated-dose toxicity: oral

The results of a repeated-dose toxicity study after oral administration are summarised in the following table.

Table 21a – Studies on repeated-dose toxicity after oral administration

Method	Results	Remarks	Reference
Rat (Sprague-Dawley) male/female 5/sex/dose Range-finding study 0, 100, 300 and 1000 mg/kg/d, oral gavage for 10 days.	All animals in the 1000 mg/kg/d group died or were killed moribund between study days 2 and 5. At 300 mg/kg/d, 1 male (study day 4) and 2 females (study days 6 and 8) were killed moribund. Additionally, there were reduced body weights and weight gains with other signs of clinical toxicity. Reduced absolute liver weights, reduced paired kidney weights and increased paired testes weights were also evident. At 100 mg/kg/d there were no clinical signs of toxicity or statistically significant adverse effects.	Range-finding study. Not recorded in the IUCLID dossier.	Reported in Unpublished (2004)
Rat (Sprague-Dawley) male/female Combined repeated dose and reproduction / developmental screening (oral gavage) 0, 5, 15 and 40 mg/kg/day: *- 10/sex/dose for 2 weeks of pre-breed exposure, 2 weeks of mating, 3 weeks each of gestation and*	The study originally used a high-dose group of 200 mg/kg/d. However, owing to excessive toxicity, this was reduced to 100 mg/kg/d. The study was again stopped because of excessive toxicity at 100 mg/kg/d and early indications of toxicity in the mid-dose group (50 mg/kg/d). The highest dose was therefore set at 40 mg/kg/d. **28-day exposure (control & high-dose groups, females)** ***40 mg/kg/d:*** Clinical signs: ataxia (3/5 females), rooting post-dosing (2/5 females; considered by the study authors to be related to taste aversion). Body weight & feed consumption: 8% ↓ in body weight, no change in feed consumption. Body weight changes during recovery were the same in treated and untreated groups but terminal body weight 7% ↓ at 40 mg/kg/d. Organ weights: 23% ↓ in absolute spleen weight, 24% ↓ in thymus weight relative to terminal brain weight. After 2-week recovery period, absolute	1 (reliable without restriction) **Test material (EC name): triphenyl phosphite**	Unpublished (2004)

Method	Results	Remarks	Reference
lactation (F0 females) *- direct dosing of F1 offspring from weaning for at least 7 weeks* 0 and 40 mg/kg/d: *- 5 F0 males/group designated as recovery animals (2 weeks without dosing after the F0 male dosing period was completed (28 days))* *- 5 females/group dosed for 28 days* *- 5 females/group dosed for 28 days followed by 2-week recovery period.* Equivalent or similar to OECD Guideline 422	weights of brain (4% ↓), thymus (30% ↑) & liver (13% ↓) were statistically significantly different from the controls; weights of thymus (40%) & heart (6%) ↑ relative to terminal body weight. No treatment-related gross findings. Histopathology: ultimobranchial cysts of the thyroid in 4/5 females (1/5 of the controls). No changes in clinical chemistry, haematology or urinalysis. Neurological effects (**for more detail see table 21b below**): in week 1, average approach response score increased, average tail pinch response score decreased. In week 4, average pupil size score reduced. In the recovery-group females, average approach response score was increased in week 2 of treatment but there was no difference in week 1 of the recovery period. **F0 (repeated-dose toxicity endpoints)** ***40 mg/kg/d:*** 2/10 females euthanized on PND 3 and 4 (litters were euthanized moribund). Clinical signs: ataxia (5/10 males; 3/10 females during pre-breed, 7/10 during gestation, 9/10 during lactation); hindlimb splay (3/10 females during gestation); foot splay (7 females during lactation). Body weight & food consumption: reduction in body weight gain of males for study days 14-21 (loss of 4.8 g compared with increase of 16.4 g in controls) and 21-28 (68% ↓) and of females for study days 7 to 14 (50% ↓). Male terminal body weight ↓ by 8%. Feed consumption of males slightly increased over study days 0 – 14. Body weight gains of males unaffected during the recovery period, although terminal body weight was reduced by 14%. Organ weights: in males, paired epididymides weight (14% ↑) and paired testis weight (7.5% ↑) statistically significantly increased relative to terminal body weight. In the recovery-group males, paired absolute testes weights significantly reduced (9%) and paired adrenal gland weight increased (11%) relative to terminal body weight. In females, absolute thymus weights ↑ (78%), absolute heart, liver & paired kidney weights ↓ (17%, 39% & 22%, respectively); relative to body weight, brain & thymus weights ↑ (27% & 126%, respectively); relative to brain weight, thymus weight ↑ (76%), liver & paired kidney weights ↓ (30% & 22%, respectively). Gross and histopathology: 5/5 males (necropsy at 28 days) exhibited chronic inflammation of the prostate (compared with 2/5 control males).		

Method	Results	Remarks	Reference
	No changes in clinical chemistry, haematology or urinalysis (males). Statistically significant ↓ in red blood cell distribution width (12.9% compared with 19.5% in controls), ↑ platelet count (1063 compared with 881 in controls) and percent eosinophils (1.2% compared with 0.2% in controls), blood chloride ↓ by 5% (females). Neurological effects (reported more fully in section 5.11): ↑ average pupil size score (females) in week 1. ↑ percent with abnormal gait and total gait score in weeks 5 to 9 (females). ***15 mg/kg/d:*** Organ weights: in females, absolute thymus weights ↑ (91%); relative (to body weight) thymus & heart weights ↑ (104% & 11%, respectively); relative to terminal brain weight, ↑ thymus weight (88%). Statistically significant ↓ in red blood cell distribution width (13.5% compared with 19.5% in controls) (females). Neurological effects (reported more fully in section 5.11): average muscle tone score ↑ in week 9 (females). ***5 mg/kg/d:*** Organ weights: in males, paired epididymides weight statistically significantly increased relative to terminal brain weight (not at higher doses). Significant increase in relative weight of seminal vesicles with coagulating glands (not at higher doses). In females, relative (to body weight) heart weights ↑ (not at 40 mg/kg/d). **F1 post-wean offspring (repeated-dose toxicity endpoints)** ***40 mg/kg/d*** No F1 animals weaned, owning to excessive toxicity. ***15 mg/kg/d (10/sex/group)*** Neurological effects (5/sex/group): no treatment-related effects. Organ weights (7 weeks post-weaning): absolute prostate weight significantly ↓ (22%), relative prostate weight (to body weight) significantly ↓ (26%). Absolute heart weight ↑ (15%) (females). Blood clinical chemistry: aspartate amino transferase ↓ (45% in males, 17% in females), alanine aminotransferase ↓ (24%, males). Haematology: mean corpuscular volume ↓ (5% males), mean corpuscular haemoglobin ↓ (8%, males); red blood cell distribution width ↑ (37%, females). Gross pathology: 1/5 males had epididymides and testes reduced in size bilaterally. Fluid-filled uterus in 2/5 females (probably owing to the females being in oestrus).		

Method	Results	Remarks	Reference
	Histopathology: 3/5 males had chronic inflammation of the prostate (2/5 of the controls). Chronic inflammation of the lung in 2/5 females, ultimobranchial cysts of the thyroid in 2/5 females. ***5 mg/kg/d (10/sex/group)*** Neurological effects (5/sex/group): no treatment-related effects (males). Organ weights: absolute liver (13%) and seminal vesicles with coagulating gland weights (30%) significantly ↑ (males). Relative prostate weight (to body weight) significantly ↓ (23%). Blood clinical chemistry: alanine aminotransferase ↓ (30%, males). Haematology: mean corpuscular volume ↓ (4%, males). Gross pathology: fluid-filled uterus in 1/5 females (probably owing to the female being in oestrus).		

Neither a 28-day (OECD 407) nor a 90-day (OECD 408) study was available in the registration dossier. Therefore, the combined OECD 422 study has been used to inform on the 28-day repeated-dose toxicity of TPP.

In a range-finding study in which TPP was administered over 10 days, severe toxicity, resulting in the death of animals, was evident at 300 and 1000 mg/kg/d within a few days of administration being started. The initial high-dose group (200 mg/kg/d) in the main study also resulted in excessive toxicity (not further described), this time during the two-week pre-breed period. As a result, the study was restarted with a maximum dose of 100 mg/kg/d. Again, excessive toxicity occurred at this dose and early indications of toxicity were recorded at the mid dose (50 mg/kg/d), resulting in termination of the study after three weeks. Subsequently, a dose of 40 mg/kg/d was chosen as the high dose.

The protocol followed in the main study exceeded the OECD 422 study design by following the F1 offspring to adulthood, with continued exposure and assessments of neurologic, immunologic and reproductive structures and functions. The protocol also assessed F0 recovery males, 28-day females and 28-day recovery males and females. The study design is shown in Appendix 3. The main dose-related effects recorded in the F0 parents and 28-day females at each dose are summarised below.

- **40 mg/kg/d**: clinical signs (ataxia, hind-limb and foot splay); decrease in body weights and body weight gains without concomitant decrease in food consumption; changes in absolute and relative organ weights; neurological effects (females); and some changes in haematology parameters (females).
- **15 mg/kg/d**: increased thymus absolute and relative weights (F0 females); and decreased red blood cell distribution width (F0 females).
- **5 mg/kg/d**: no dose-related effects.

Neurotoxicity was identified as one of the grounds for concern.

The investigation of neurological effects is a specific end point of the OECD 422 assay, as reported in sections 5.6, 5.9 and 5.10. Functional observation battery (FOB) investigations were performed on F0 male and female rats (10/sex/group), and on females treated for 28 days (5/sex/group) and recovery animals (half-way through the recovery period). FOB was also performed on F1 offspring mid-way through the post-wean period (5/sex/group); the grip strength of the same animals was determined in the last week of the post-wean period. Treatment-related observations are reported below.

Table 11b - Summary of functional observation battery findings in a combined repeated-dose toxicity / reproductive toxicity OECD 422 screening study. (Only observations for which there was a treatment-related effect are reported; results given as mean ± SD).

mg/kg/d	0	5	15	40
28-day-exposed & recovery groups (females, n = 5)				
SENSORY & NEUROMUSCULAR OBSERVATIONS				
Average approach response score Week 1	1.8 (± 0.2)			3.6 (± 0.4)
Average tail pinch response score Week 1	3.6 (± 0.2)			2.2 (± 0.2)
Average pupil size score Week 4	2.2 (± 0.2)			1.2 (± 0.2)
Average approach response score Recovery group, week 2 of treatment	1.2 (± 0.2)			2.8 (± 0.5)
F0 Females (n = 10)				
SENSORY & NEUROMUSCULAR OBSERVATIONS				
Average pupil size score Week 1	1.2 (± 0.1)	1.5 (± 0.2)	1.3 (± 0.2)	1.8 (± 0.1)
HOME-CAGE OBSERVATIONS				
Abnormal gait (%)				
Week 5	0	0	0	30
Week 6	0	0	0	20
Week 7	0	0	0	44[a]
Week 8	0	0	0	33[b]
Week 9	0	0	0	0[c]
Abnormal total gait score (%)				
	0	0	0	30
Week 5	0	0	0	20
Week 6	0	0	0	44[a]
Week 7	0	0	0	33[b]
Week 8	0	0	0	0[c]
Week 9				
OPEN FIELD OBSERVATIONS				
Abnormal gait (%)				
Week 5	0	0	0	30
Week 6	0	0	0	40
Week 7	0	0	0	67[a]
Week 8	0	0	0	100[b]
Week 9	0	0	0	100[c]
Abnormal total gait score (%)				
	0	0	0	70
Week 5	0	0	0	50
Week 6	0	0	0	100[a]
Week 7	0	0	0	100[b]
Week 8	0	0	0	100[c]
Week 9				
HANDLING OBSERVATIONS				
Average muscle tone score Week 9	3.2 (± 0.1)	3.3 (± 0.2)	4.0 (± 0)[d]	4.0 (± 0)[c]

[a] n = 9; [b] n = 3; [c] n = 2; [d] n = 8

Several FOB parameters were affected by oral, repeated-dose administration of 40 mg/kg/d TPP to rats.

During the first week of exposure, sensory and neuromuscular effects were observed in females at 40 mg/kg/d: increased average approach response score (1 = no response, 2 = normal, 3 = animal pulls away slightly or jumps and turns away, 4 = animal freezes); decreased average tail pinch score (score 2 = indifference, 3 = freezing, 4 = normal); and decreased average pupil size score (score 1 = constricted, 2 = normal, 3 = dilated). An increased average response score was also recorded during the recovery period following 28 days of exposure. In females exposed for 28 days, the average pupil size score was decreased (1 = constricted, 2 = normal, 3 = dilated).

Effects on the gait of F0 females were apparent from week 5 of administration of 40 mg/kg/d and progressively worsened, such that ataxia was so severe during lactation that FOB testing could not be performed on seven animals. Average muscle tone score was increased (3 = normal, 4 = moderate resistance) during week 9 in the mid-dose group but as only two females of the high-dose group were available at this time-point, it is not possible to conclude if this was a dose-related effect.

No adverse neurological effects were reported in the F1 offspring, and there were no statistically significant differences between any treated and untreated animals in investigations into auditory startle, motor activity and grip strength.

Additionally the Registrant(s) submitted the results of a literature search that had been conducted in 2009 which the eMSCA considered. Although several studies have investigated the neurotoxic potential of TPP, only three have used oral administration and one dermal administration, all in hens. The NOAEL for neurotoxicity following a single oral administration was reported to be < 250 mg/kg; after a single dermal exposure with 50 mg/kg, there was reported to be some indication of neuropathology in 1 of 3 birds. There was no information provided on the nature of the neurotoxicity or pathology. *In vitro* investigations in human monocytes, rat brain and bovine adrenal cells revealed different actions: carboxylesterase inhibition, neurotoxic esterase inhibition, inhibition of catecholamine secretion, mitochondrial changes. Several other studies used non-standard routes of administration (sub-cutaneous, intra-venous) and / or animal species and so are of limited value. Overall, insufficient information was presented on these additional studies to draw conclusions about the neurotoxic potential of TPP *in vivo* by relevant routes of exposure in species of relevance to humans.

Repeated-dose toxicity: inhalation

No information available.

Repeated-dose toxicity: dermal

No information available.

Repeated-dose toxicity: other routes

No information available.

Human information

No information available.

Summary and discussion of repeated-dose toxicity

The repeated-dose toxicity of TPP has been investigated in a combined repeated-dose toxicity study with the reproduction / developmental toxicity screening test (OECD 422),

by the oral route. No information is available on other routes of exposure. The amount of information provided by the registrants in the registration dossier was insufficient for an evaluation; therefore, the eMSCA obtained the full study report from the registrants and used this as the basis of its assessment.

The study report of the OECD 422 study also referred to a range-finding study conducted over 10 days, in which toxicity was observed at 1000 and 300 mg/kg/d but not at 100 mg/kg/d. In the range-finding study, 10/10 animals died or were killed moribund within five days of a dose of 1000 mg/kg/d being administered. In the mid-dose group of 300 mg/kg/d, 3/10 animals were killed moribund between study days 4 and 8.

In the OECD 422 study, excessive toxicity (not further described) resulted in study termination within two weeks of 200 mg/kg/d being administered and after three weeks of 100 mg/kg/d being administered. Furthermore, in accordance with the criteria for classification as STOT-RE, significant functional changes in the central or peripheral nervous systems were observed when a dose of 40 mg/kg/d was administered for 28 days. When the administration period was extended to 70 days (F0 females), ataxia was so severe that FOB testing could not be performed on the majority of animals. Adjustment of the oral guidance value for classification as STOT-RE 2 (≤ 100 mg/kg/d based on a 90-day study) gives an equivalent guidance value for a 28-day study of ≤ 300 mg/kg/d. The adult systemic toxicity observed at doses equal to and below this value is thus considered to meet the criteria for classification of TPP for STOT-RE 2 – H373 (nervous system).

The registrants identified a NOAEL for male and female systemic toxicity of 15 mg/kg/d from the OECD 422 study, based on the effects at the LOAEL of 40 mg/kg/d: reductions in body weights and body weight gains; ataxia and lethargy; significantly increased relative paired adrenal-gland weight; significantly reduced absolute paired testis weights. However, significant increases in absolute and relative thymus weights were observed in females at 15 mg/kg bw/d (absolute weight ↑91%; relative (to brain) weight ↑88%). Although there were no histopathology findings in this organ, it is considered to be an adverse effect due to the magnitude of the increase. Therefore, 15 mg/kg/d is regarded as the LOAEL and 5 mg/kg/d as the NOAEL for this end-point. The range-finding study combined with the definitive study, in particular the inclusion in the latter of dose groups that had to be terminated because of excessive toxicity, provided clear evidence that TPP administered by gavage caused progressive systemic toxicity (excessive toxicity when administered at lower doses for longer durations, the worsening over time of reductions in body weight and body weight change, and of ataxia and foot splay). Considering the progressive toxicity, this lower NOAEL will also provide additional reassurance in the extrapolation from a 28-day study to a longer-term duration of exposure for the DNEL derivation.

Therefore, as a reliable short-term toxicity study (28 days) is available showing severe toxicity effects, for which the observed NOAEL-28 days, with the application of an appropriate uncertainty factor, allows the extrapolation towards the NOAEL-90 days for the same route of exposure, no further information is required to clarify the concern for neurotoxicity. The eMCSA proposes that a CLH proposal is taken forward to classify TPP as STOT RE 2.

Comments and observations for the Registrant(s)

More detail of the OECD 422 study should be added to the RSS, including information on the range-finding study. Consideration should be given to using the NOAEL identified in this evaluation.

7.8.5. Mutagenicity

Mutagenicity was not identified as an area of concern. However, because the registration dossier did not include sub-chronic (90-day) or two-year carcinogenicity studies, this end-

point was evaluated to inform on the carcinogenic potential of TPP. The full study reports for the unpublished studies were provided by the registrants.

Non-human information

In vitro data

The results of *in vitro* genotoxicity studies are summarised in the following table. It is noted that the test material identity in the relevant IUCLID endpoint study records was incorrect. However, the registrants confirmed that the tests had been conducted on TPP.

Table 22. *In vitro* genotoxicity studies

Method	**Results**	**Remarks**	**Reference**
Bacterial reverse mutation assay (Ames test) (gene mutation) *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA 1538 (with and without metabolic activation) Test doses: 0, 10, 100, 500, 1000, 5000 µg/plate. Equivalent or similar to OECD Guideline 471 (Bacterial Reverse Mutation Assay). Duplicates of each dose. Appropriate positive controls and vehicle-treated negative included.	The test was reported to be: negative in all strains with and without metabolic activation; There was no cytotoxicity up to 5000 µg/plate.	1 (reliable without restriction) **Test material (EC name): triphenyl phosphite**	Unpublished (1980b)
Bacterial reverse mutation assay (Ames test) (gene mutation) *S. typhimurium* TA 1535, TA 1537, TA 98 and TA 100 (with and without metabolic activation); there was discrepancy in the dossier as to whether or not TA 1538 was also included. Test doses: 0, 100, 333, 1000, 3333, and 10000 µg/plate. Equivalent or similar to OECD Guideline 471 (Bacterial Reverse Mutation Assay). Tested in triplicate at each concentration and experiment repeated.	The test was reported in the IUCLID dossier to be: negative in all strains without metabolic activation; ambiguous in all strains with metabolic activation. There was no cytotoxicity up to 10000 µg/plate.	2 (reliable with restrictions) **Test material (EC name): triphenyl phosphite**	Zeiger *et al.* (1987)

Method	Results	Remarks	Reference
Appropriate positive controls for the system without metabolic activation and vehicle-treated negative included. The positive control for the system with metabolic activation was stated to be 9-aminoacridine.			
DNA repair-suspension assay (DNA damage and/or repair) *Escherichia coli* tester strains W3110 (pol A+) and p3478 (pol A-) (with and without metabolic activation). Test concentrations: 0, 0.1, 1, 5, 10, and 50 µg/mL Method based on Slater *et al*. (1971) Cancer Res. 31:970-973.	The test was reported to be: negative with and without metabolic activation TPP was concluded not to cause preferential killing of the repair-deficient strain. No cytotoxicity up to 50 µg/mL with or without metabolic activation.	2 (reliable with restrictions) **Test material (EC name): triphenyl phosphite**	Unpublished (1980a)
Studies provided following initial evaluation			
Bacterial reverse mutation assay *Salmonella typhimurium* strains: TA1537, TA1535, TA98, TA100 and TA102 Test doses: 0, 0.15625, 0.3125, 0.625, 1.25, 2.5 and 5.0 µL/plate. OECD Guideline 471 (Bacterial Reverse Mutation Assay) Full study report seen.	Negative (with and without metabolic activation)	1 (reliable without restriction) **Test material (EC name): triphenyl phosphite**	Unpublished (2017a)
Mammalian cell gene micronucleus test	Negative (with and without metabolic activation)	1 (reliable without restriction) **Test material (EC name): triphenyl phosphite**	Unpublished (2017b)

The initial data package evaluated by the eMSCA contained two Ames tests, both of which were conducted prior to the current 1997 OECD 471 guideline. It was noted, therefore, that in neither assay did the battery of strains tested include *E. coli* WP2 uvrA, *E. coli* WP2 uvrA (PKM101), or *S. typhimurium* TA 102. OECD guideline 471 (1997) recommends that

one of these strains should be included in addition to *S. typhimurium* strains TA1535, TA1537/TA97a/TA97, TA98 and TA100. These latter strains have GC base pairs at the primary reversion site and are recognised not to detect certain oxidising mutagens and cross-linking agents. *E. coli* WP2 strains and *S. typhimurium* TA 102 have an AT base pair at the primary reversion site and are able to detect both these types of mutagens. Instead, *S. typhimurium* TA1538 was included in the first assay (and possibly the second, although this is not clear from the dossier, as it was not listed as a tested strain but was mentioned in the results). *S. typhimurium* TA1538 is not a validated strain for the current version of OECD 471 and duplicates the coverage of TA 98, which was also included in the assays. Furthermore, it was noted that only duplicates of each test concentration were run in the first assay, whereas the test guideline stipulates that triplicates should be run at each dose, unless a scientific justification is provided for duplicate testing.

Both assays were reported in the dossier to give ambiguous results with metabolic activation, but the reasons for this conclusion were not given; consultation of the study report of the first assay (Unpublished (1980b)) indicated that the results both with and without metabolic activation were clearly negative. In the second assay the positive control substance for the system with metabolic activation was stated to be 9-aminoacridine for all strains; however, this substance is used for assays without metabolic activation and is not a suitable positive control substance for assays with metabolic activation.

The third *in vitro* assay was also conducted in bacterial cells. This DNA repair/damage assay is based on the principle that greater toxicity of a test substance in DNA-deficient strains than in their repair-proficient counterparts serves as an indicator of DNA damage. This is a non-standard assay that does not have an OECD guideline. It is also not included in the REACH guidance on information requirements. TPP was negative for DNA damage in this assay.

Following the initial evaluation, the eMSCA requested that the registrant conduct an *in vitro* micronucleus assay and a bacterial reverse mutation assay to enhance the robustness of the genotoxicity package.

The bacterial reverse mutation assay was conducted in accordance with OECD 471 and GLP. All strains tested (TA1537, TA1535, TA98, TA100 and TA102) were negative in the presence and absence of metabolic activation. The *in vitro* micronucleus assay was conducted in accordance with OECD 487 and GLP. In this study, TPP did not show any potential to induce micronuclei or clastogenic or aneugenic potential in cultured human peripheral blood lymphocytes, both in the presence and absence of metabolic activation.

Overall, the *in vitro* data are negative.

Comments and observations for the Registrant(s)

The positive control substance used for the assay with metabolic activation in the study by Zeiger *et al.* (1987) (section 7.6.1. of the IUCLID dossier) should be verified. It should also be clarified whether or not TA1538 was included as one of the test strains in this assay.

In vivo data

One *in vivo* genotoxicity study was reported in the registration dossier, as summarised in the following table.

Table 23. *In vivo* genotoxicity study

Method	Results	Remarks	Reference
Micronucleus assay (chromosome aberration) Mouse (CD-1) 5/sex/dose Oral: gavage, two single doses administered 24 hours apart. Sacrifice 6 hours after second dose, bone marrow sampled. 0, 1250, 2500, and 5000 mg/kg (total dose) Equivalent or similar to OECD Guideline 474 (Mammalian Erythrocyte Micronucleus Test). Appropriate positive and vehicle-treated control groups.	Genotoxicity: negative (male/female). Toxicity was observed at 5000 mg/kg: 3 males & 2 females died within 48 hours; tremors observed 30 minutes after dosing.	1 (reliable without restriction) **Test material (EC name): triphenyl phosphite**	Unpublished (1981)

An *in vivo* micronucleus assay is available. Although the NCE/PCE ratio was not affected by the administration of TPP and no toxicokinetic studies are available, the death of 5/10 animals at 5000 mg/kg indicated that the maximum tolerated dose had been exceeded and it is therefore assumed that TPP was systemically available. From the effects on haematology parameters observed in the OECD 422 study (section 7.8.4), it is also assumed that TPP reached the bone marrow. Because of these deaths, only two males and three females were sampled in the high-dose group; however, there was no increase in the number of micronucleated cells per 1000 polychromatic erythrocytes in any of the dose groups. It is noted that only one sampling time was used, this being six hours after the second dose administration. OECD guideline 474 (1997) states that, when two or more doses are administered at 24-hour intervals, samples of bone marrow should be collected between 18 and 24 hours after the final treatment.

In conclusion, TPP tested negative in the *in vivo* micronucleus study, but with limitations.

Comments and observations for the Registrant(s)

In section 7.6.2. of IUCLID, it should be clarified what doses were used for the preliminary study and what for the main study. The sub-section on 'any other information on materials and methods' states that doses of 0, 4450, 9100 and 18200 mg/kg were used in the main study, but other parts of the study summary indicate that the doses were 0, 1250, 2500 and 5000 mg/kg. Were the former doses used in the preliminary study?

It is noted that in section 7.6.2., sub-section 'any other information on results', the table gives doses of TDP, not TPP. The identity of the test substance should be clarified or rectified if it is a mistake.

Additionally the table of results should be amended as the second and third headings are the wrong way round: the values given for the PCE/NCE ratio are actually the number of micronucleated cells per 1000 polychromatic erythrocytes. The study report provides a NCE/PCE ratio, whereas the same values are reported in the dossier as the PCE/NCE ratio – this should be corrected.

Human information

No information available.

Summary and discussion of mutagenicity

Four of the five *in vitro* tests included in the latest update of the registration dossier were conducted in bacteria. Two of these studies were conducted according to an old OECD guideline that did not use all of the currently-recommended strains of bacteria, and one was a non-standard assay that does not have an OECD guideline. However, the most recent study in bacteria (bacterial reverse mutation test) was conducted according to the latest version of the OECD guideline (OECD 471) and GLP. No deficiencies were noted. In this study, TPP did not induce any significant increases in the number of revertants in the five tester strains in the presence or absence of metabolic activation.

Following a request from the eMSCA, the registrants submitted an *in vitro* micronucleus assay. This study was conducted according to OECD 487 and GLP. In this study, TPP did not show any potential to induce micronuclei or clastogenic or aneugenic potential in cultured human peripheral blood lymphocytes, both in the presence and absence of metabolic activation.

In the available *in vivo* micronucleus assay, a number of deficiencies were noted. Excessive toxicity in the high-dose group limited the number of animals sampled at this dose, although the number of micronuclei was not increased in the surviving animals nor the low- and mid-dose groups. Furthermore, the bone marrow was investigated at a shorter time-point than recommended in the OECD test guideline.

The package of genotoxicity studies therefore investigated mutation in bacterial cells; DNA damage in bacterial cells; clastogenicity and aneuploidy in mammalian cells *in vitro*; and clastogenicity in mammalian cells *in vivo*. These tests were all negative. Although some of these tests have limitations, there is no residual concern for genotoxicity based on the available data.

7.8.6. Carcinogenicity

Carcinogenicity was not identified as an area of concern, but a brief summary has been included for completeness.

Carcinogenicity data

No data are available.

Summary and discussion of carcinogenicity

Neither a sub-chronic nor chronic repeated-dose study was submitted in the registration dossier. The only repeated-dose study was a combined repeated-dose/reproductive screening test, in which TPP was administered for 28 days in adult male and female rats, 70 days in F0 females and 49 days in F1 offspring (direct dosing, excluding pre-natal and lactational exposure). No effects of concern for carcinogenicity (hyperplasia, pre-neoplastic lesions) were observed in this study. TPP was non-genotoxic in *in vitro* bacterial assays, an *in vitro* micronucleus assay in human lymphocytesand an *in vivo* micronucleus assay. Overall, the available data on TPP do not raise any concerns for carcinogenicity.

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

Reproductive toxicity was identified as one of the grounds for concern for TPP.

As mentioned in section 7.8.4, the combined repeated-dose toxicity with the reproduction/developmental toxicity screening test (OECD 422) informed on the reproductive toxicity of TPP; these effects are presented in the table below.

Table 24. Study on reproductive toxicity after oral administration

Method	Results	Remarks	Reference
Rat (Sprague-Dawley) male/female Combined repeated dose and reproduction / developmental screening (oral: gavage) 0, 5, 15 and 40 mg/kg/day: *- 10/sex/dose for 2 weeks of pre-breed exposure, 2 weeks of mating, 3 weeks each of gestation and lactation (F0 females)* *- direct dosing of F1 offspring from weaning for at least 7 weeks* 0 and 40 mg/kg/d: *- 5 F0 males/group designated as recovery animals (2 weeks without dosing after the F0 male dosing period was completed (28 days)* *- 5 females/group dosed for 28 days* *- 5 females/group dosed for 28-days followed by 2-week recovery period.* Equivalent or similar to OECD Guideline 422	The study originally used a high-dose group of 200 mg/kg/d. However, owing to excessive toxicity, this was reduced to 100 mg/kg/d. The study was again stopped because of excessive toxicity at 100 mg/kg/d and early indications of toxicity in the mid-dose group (50 mg/kg/d). The highest dose was therefore set at 40 mg/kg/d. At 40 mg/kg/d, 2/10 females euthanized on PND 3 and 4 (litters were euthanized moribund). ***Maternal toxicity*** Clinical signs: ataxia (3/10 females during pre-breed, 7/10 during gestation, 9/10 during lactation); hindlimb splay (3/10 females during gestation); foot splay (7 females during lactation) at 40 mg/kg/d. Maternal body weight gains: at 40 mg/kg/d, reduced by 29% during pre-breed, 38% during gestation, 85% post-natal days 0 to 4. Overall body weight gain during lactation greater than controls. No difference in feed consumption from controls during pre-breed, 10% reduction during gestation, no change during lactation. Organ weights: at 40 mg/kg/d absolute thymus weights ↑ , absolute heart, liver & paired kidney weights ↓ ; relative to body weight, brain & thymus weights ↑ ; relative to brain weight, thymus weight ↑ , liver & paired kidney weights ↓ . At 15 mg/kg/d, absolute thymus weights ↑ ; relative (to body weight) thymus & heart weights ↑ ; relative to terminal brain weight, ↑ thymus weight. Neurological effects (FOB parameters) at 40 mg/kg/d that worsened during gestation and lactation. Statistically significant ↓ in red blood cell distribution width, ↑ platelet count and percent eosinophils, blood chloride ↑ (females) at 40 mg/kg/d. ↓ in red blood cell distribution width at 15 mg/kg/d. ***Reproductive effects*** No significant effects on F0 mating, fertility, gestational or pregnancy indices. No statistically significant effect on number of total implantation sites per litter and the number of total and live pups per litter at birth, nor on the number of dead pups at birth. Post-implantation loss per litter was	1 (reliable without restriction) key study experimental result **Test material (EC name): triphenyl phosphite**	Unpublished (2004)

<table>
<tr><th>Method</th><th>Results</th><th>Remarks</th><th>Reference</th></tr>
<tr><td></td><td>increased with TPP but not in a dose-related manner (2.5, 10.4, 7.7, 10.1 at 0, 5, 15, 40 mg/kg/d). The number of live pups/litter was significantly reduced at birth (post-natal day 0) at 40 mg/kg/d (see table below), largely as a result of a decrease in the total number of pups born at this dose (15.9, 14.6, 15.3, 12.9 at 0, 5, 15, 40 mg/kg/d) and the slightly reduced number of implantation sites per litter (15.8, 16.1, 16.4, 14.3 at 0, 5, 15, 40 mg/kg/d, not statistically significant); these figures were influenced by three dams, two of which had only 8 and 10 implantation sites, respectively, and one of which had 15 implantation sites but delivered only 6 pups.

Developmental effects

No significant effect on live-birth nor still-birth indices. Survival indices for PND 0-4 & 7-14 reduced at 40 mg/kg/d. Two dams lost their entire litters (one on PND 3, one on PND 4). Mean number of live pups per litter for PND 0, 4, 14, 21 reduced at 40 mg/kg/d. The number of live litters at PND 21 was reduced in a dose-related fashion. These findings are summarised below (statistically significant findings in italics).

<table>
<tr><th></th><th colspan="4">mg/kg/d</th></tr>
<tr><th></th><th>0</th><th>5</th><th>15</th><th>40</th></tr>
<tr><td>Survival index PND 0-4</td><td>98.7</td><td>98.6</td><td>100</td><td>71.4</td></tr>
<tr><td>Survival index PND 4-7</td><td>100</td><td>100</td><td>100</td><td>86.3</td></tr>
<tr><td>Survival index PND 7-14</td><td>100</td><td>100</td><td>100</td><td>95.4</td></tr>
<tr><td>Survival index PND 14-21</td><td>100</td><td>97.8</td><td>100</td><td>100</td></tr>
<tr><td>Survival PND 4-21</td><td>100</td><td>97.8</td><td>100</td><td>82.5</td></tr>
<tr><td>Mean live pups/litter PND 0</td><td>15.9</td><td>14.4</td><td>14.8</td><td>12.4</td></tr>
<tr><td>Mean live pups/litter PND 4</td><td>15.7</td><td>14.2</td><td>14.8</td><td>9.3</td></tr>
<tr><td>Mean live pups/litter PND 7</td><td>10</td><td>10</td><td>10</td><td>8.7</td></tr>
<tr><td>Mean live pups/litter PND 14</td><td>10</td><td>10</td><td>10</td><td>8.3</td></tr>
<tr><td>Mean live pups/litter PND 21</td><td>10</td><td>9.8</td><td>10</td><td>8.3</td></tr>
</table>
</td><td></td><td></td></tr>
</table>

Method	Results	Remarks	Reference

Number live litters PND 21	10	9	8	7

Number of pups found dead during lactation were PND 0-4: 2, 3, 4, 39 (plus 5 on PND 3 and 1 on PND 4 killed moribund); PND 5-21: 0, 2, 0, 1 (plus 3 killed moribund) at 0, 5, 15, 40 mg/kg/d, respectively. Pups killed moribund were cold to the touch, had no milk in stomach, emaciated, partially cannibalised and/or with limb swollen from apparent infection.

Mean pup body weights per litter (% of control value) are shown in the table below (statistically significant findings in italics).

Mean pup body wt/litter	**0**	**5**	**15**	**40**
PND 0	100	97.9	100	91
PND 4	100	100	100	*80*
PND 7	100	98	100	*75*
PND 14	100	97	100	*78*
PND 21	100	97	100	*83*

Necropsy of F1 offspring (PND 21)

All surviving F1 pups at 40 mg/kg/d were euthanized without necropsy, owing to excessive maternal and offspring toxicity in this group.

Pup organ weights at PND 21: absolute paired epididymides weights significantly reduced (by 12% & 13% at 5 & 15 mg/kg/d, respectively), also relative to body weight (by 8% & 14%, respectively) and brain weight (by 10% & 14%, respectively). No effects on female pup organ weights.

There were no other dose-related necropsy findings.

F1 post-wean offspring (7 weeks post-wean: PNDs 22 to 71)

10 F1 per sex per group at 0, 5 and 15 mg/kg/d were evaluated. No F1 animals at 40 mg/kg/d were weaned.

Body weights: no differences between groups.

Neurological effects (5/sex/group): no treatment-related effects.

Organ weights: absolute prostate weight significantly ↓ (15 mg/kg/d), relative prostate weight (to body weight) significantly ↓ (5 & 15 mg/kg/d). Absolute heart weight ↑ (females, 15 mg/kg/d).

Method	Results	Remarks	Reference
	Blood clinical chemistry at 15 mg/kg/d: aspartate amino transferase ↑ , alanine aminotransferase ↓ (males, also at 5 mg/kg/d). Haematology: mean corpuscular volume ↓ (also at 5 mg/kg/d), mean corpuscular haemoglobin ↓ (males); red blood cell distribution width ↑ (females). Gross pathology: 1/5 males at 15 mg/kg/d had epididymides and testes reduced in size bilaterally. Fluid-filled uterus in 1/5 and 2/5 females at 5 & 15 mg/kg/d, respectively (probably owing to the females being in oestrus). Histopathology (15 mg/kg/d): 3/5 males had chronic inflammation of the prostate (2/5 of the controls). Chronic inflammation of the lung in 2/5 females, ultimobranchial cysts of the thyroid in 2/5 females. F1 male age at acquisition of preputial separation was unaffected. F1 age at acquisition of vaginal patency was equivalent across groups. No significant differences amongst groups for body weights and body weight gains during the post-wean period (males and females). Sperm parameters were unaffected.		

Effects on fertility

Non-human information

There were no effects on male or female reproductive indices in an OECD 422 study. Precoital interval and gestational length were unaffected, as were sperm parameters and histopathology of the male reproductive organs. The numbers of live pups per litter were statistically significantly reduced at birth at 40 mg/kg/d, largely because of a slightly reduced number of implantation sites per litter and slightly increased post-implantation loss (neither effect statistically significant). These values were influenced by two dams that had a reduced number of implantation sites and one that had increased post-implantation loss. Overall, however, there was not a consistent adverse effect on reproduction.

Human information

No information available.

Developmental toxicity

Non-human information

Offspring toxicity was evident during lactation in the 40 mg/kg/d group. Survival indices, numbers of live pups/litter and pup body weights were reduced and pup mortality was increased at various time points throughout lactation. All pups in two litters of the 40 mg/kg/d group died on PND 3-4.

Maternal toxicity was also evident at 40 mg/kg/d and worsened as the duration of exposure increased. In particular, indications of neurotoxicity became progressively worse, such that during lactation ataxia was so severe in seven animals that FOB testing could not be performed. Maternal body weight gains were also reduced in the high-dose group throughout the pre-breed period, gestation and PND 0-4. Of the two dams (numbers 58

and 82) that lost their entire litters on PND 3-4, both had impaired gait scores, with the gait of dam number 58 being totally impaired, such that some FOB measurements could not be taken. Other findings in this dam were a reduced body weight (227.3 g compared with the group mean of 257.8), an agitated posture and other neurotoxicological effects (increased muscle tone, reduced approach response, reduced tail pinch response, foot splay). The litter weight at birth of this dam was 4.64 g, compared with a group mean of 5.52 g per litter; this dam also had the highest number of dead pups at birth (3 dead, 13 live). Dam number 82 had a somewhat impaired gait, a body weight that was slightly below the group mean (251.2 g), alopecia and foot splay. The litter weight at birth of this dam was 5.15 g per litter.

There was no evidence of offspring toxicity in the low- or mid-dose groups. There were also no clinical signs of maternal toxicity in these groups, but absolute and relative thymus weights were increased and the red blood cell distribution width was decreased. Extension of the TPP administration to F1 pups of the low- and mid-dose groups for seven weeks post-weaning did not result in increased toxicity compared with administration until PND 21, nor with F0 adults.

All F1 adults were subjected to a complete gross necropsy that included examination of the external surfaces, all orifices, the carcass, the thoracic, abdominal and pelvic cavities and their viscera, and cervical tissues and organs. Non-selected F1 weanlings were subjected to a complete gross necropsy (external and visceral) examination. Full histopathology was performed on all retained organs from five randomly-selected F1 adult males and females in the control and 15 mg/kg/d groups; special emphasis was placed on the stages of spermatogenesis in the male gonads and histopathology of the interstitial testicular structure. There was no evidence of developmental toxicity at 15 mg/kg/d; necropsy was not performed on the pups of the 40 mg/kg/d group.

Human information

No information available.

Summary and discussion of reproductive toxicity

The reproductive toxicity of TPP has been investigated in a single, combined repeated-dose toxicity study with the reproduction/developmental toxicity screening test (OECD 422). Reproduction parameters were unaffected and there were no reported variations, malformations or anomalies, but offspring toxicity was evident at 40 mg/kg/d.

The OECD 422 guideline states that 'this test does not provide complete information on all aspects of reproduction and development. In particular, it offers only limited means of detecting post-natal manifestations of prenatal exposure, or effects that might be induced during post-natal exposure. Due to the selectivity of the end-points, and the short duration of the study, this method will not provide evidence for definite claims of no reproduction/developmental effects.'

In the unpublished study, the duration of exposure was continued throughout lactation and until seven weeks post-lactation, so to some extent the deficits of the OECD 422 study were mitigated. The short pre-mating exposure of males (two weeks, compared with 10 weeks in an OECD 416 two-generation reproduction study) means that fertility might not be a sensitive indicator of testicular toxicity; the OECD 422 guideline states that a detailed histological examination of the testes is thus essential. The study on TPP provided further reassurance that male fertility was not affected, since it extended administration to F1 males for seven week post-weaning, followed by investigations of the stages of spermatogenesis in the male gonads and histopathology of interstitial testicular cell structure. The OECD 422 study protocol includes external and visceral gross examinations (with special attention to the organs of the reproductive system) and histopathology of retained organs, but does not include examination for skeletal alterations. Unlike the OECD

414 prenatal developmental toxicity study, the OECD 422 study includes neurological effects as a specific endpoint.

Offspring toxicity was evident at 40 mg/kg/d, with reductions in survival indices, numbers of live pups/litter and pup body weights, and increased pup mortality during lactation. However, the toxicity to pups occurred in conjunction with severe maternal toxicity at this dose, which included reductions in body weight gains during the pre-breed period, gestation and PND 0-4. Notably, 9/10 females had ataxia during lactation, with the effect being so severe in seven animals that FOB testing was not possible. The nature of the effects on the pups and dams is suggestive of the toxicity being of the same nature as the adult toxicity or secondary to maternal toxicity; in particular, it is likely that severe ataxia during lactation resulted in the ability of the dams to care adequately for their pups being compromised. Furthermore, in the absence of severe maternal toxicity (low- and mid-dose groups), there were no developmental or offspring effects. As there were no pups of the 40 mg/kg/d group available for post-wean exposure, it was not possible to monitor progressive toxicity in this group, but F1 adults of the low- and mid-dose groups exhibited a similarly low level of toxicity (including an absence of neurotoxicity) as the F0 animals that received the same doses. The available evidence therefore indicates that F1 animals exposed prenatally and potentially through lactation were not more sensitive than the F0 animals that began their exposure as adults. Overall, it is concluded that the offspring toxicity was secondary to severe maternal toxicity or of the same nature as the adult toxicity and was not indicative of a specific effect on development.

The registrants identified the following NOAELs: 15 mg/kg/d for F0 adult systemic toxicity; ≥ 40 mg/kg/d for reproductive toxicity (fertility impairment); 15 mg/kg/d for F1 (toxicity during lactation, male and female systemic toxicity that was not related to reproduction or development end-points). In the CSR the NOAEL for development is identified as 40 mg/kg/d. The US EPA reviewed TPP for its High Production Volume Chemical Challenge Program[11]. From the same study, the EPA identified the same NOAELs as the registrants.

As noted in section 7.8.4, there were treatment-related effects in the parents at 15 mg/kg/d. A NOAEL of 5 mg/kg/d has therefore been identified for adult systemic toxicity. The other NOAELs identified were ≥ 40 mg/kg/d for fertility impairment and 15 mg/kg/d for offspring toxicity.

On the basis of the information available at the time of this substance evaluation the concern for reproductive toxicity has been clarified, since there was no indication of a specific effect on fertility or developmental toxicity.

7.10. Hazard assessment of physico-chemical properties

TPP has a low melting point (ca 25°C), high boiling point (>350°C) and consequently a low volatility (<0.1 Pa at 25°C). It rapidly hydrolyses to form phenol and phosphorous acid.

Based on the available data, TPP does not meet the criteria for classification for any physico-chemical endpoints.

[11] http://www.epa.gov/hpv/pubs/summaries/ppipcc/c13182rr2.pdf

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

Table 25. Summary of the corrected dose descriptors and DNELs/DMELs calculated by the eMSCA.

Exposure pattern	Route	DNEL / DMEL	Corrected Dose descriptor	Most sensitive endpoint	Justification
Acute - local effects	Dermal	DNEL not proposed	Qualitative assessment	Sensitisation (skin)	Based on LLNA EC3. The eMSCA proposes to use a qualitative approach. See discussion.
Long-term - systemic effects	Dermal	0.0083 mg/kg/d * 0.016 mg/kg/d ^ 0.083 mg/kg/d #	NOAEL: 5 mg/kg/d (based on AF of 600)	Repeated-dose toxicity	See discussion.
Long-term - systemic effects	Inhalation	0.029 mg/m^3/8 hr	NOAEC: 4.41 mg/m^3/8 hr (based on AF of 150)	Repeated-dose toxicity	See discussion.
Long-term - local effects	Dermal	DNEL not proposed	Qualitative assessment	Sensitisation (skin)	Based on LLNA EC3. Substance will be classified as skin irritant and skin sensitiser. The eMSCA proposes to use a qualitative approach.
Acute - local effects	Dermal	DNEL not proposed	Qualitative assessment	Sensitisation (skin)	Based on LLNA EC3. The eMSCA proposes to use a qualitative approach. See discussion.
Long-term - systemic effects	Oral	0.004 mg/kg/d	NOAEL: 5 mg/kg/d (based on AF of 1200)	Repeated dose toxicity	The registrants concluded that oral exposure to the general population is not anticipated based on rapid hydrolysis and low bioaccumulation potential. See discussion for the eMSCAs analysis.
Long-term - systemic effects	Inhalation	0.007 mg/m^3/24 hr	NOAEC: 2.17 mg/m^3/24 hr (based on AF of 300)	Repeated dose toxicity	Extrapolated from oral study. See discussion.

Exposure pattern	Route	DNEL / DMEL	Corrected Dose descriptor	Most sensitive endpoint	Justification
Long-term - systemic effects	Dermal	0.004 mg/kg/d * 0.008 mg/kg/d ^ 0.042 mg/kg/d #	NOAEL: 5 mg/kg/d (based on AF of 1200)	Repeated dose toxicity	Extrapolated from oral study. See discussion.
Long-term - local effects	Dermal	DNEL not proposed	Qualitative assessment	Sensitisation (skin)	Based on LLNA EC3. The eMSCA proposes to use a qualitative approach. See discussion.

*based on 100% dermal absorption
^based on 50% dermal absorption
#based on 10% dermal absorption

DN(M)ELs for workers: discussion

Acute exposures – systemic effects

No evaluation of $DNEL_{acute}$ for systemic effects has been performed, since the acute systemic toxicity of TPP is low and a specific acute systemic hazard by the inhalation and dermal routes has not been identified.

Acute and long-term exposures – local effects

Dermal route of exposure (workers)

The following general approach to the characterisation of dose-response relationships from LLNA data is recommended (European Chemicals Agency [ECHA] (2010)):

1. a qualitative approach (by the use of potency categorisation) to define the risk management measures (RMMs) and operational conditions (OCs); and,
2. setting a DNEL (if possible) to judge the remaining likelihood of risks after these RMMs and OCs have been implemented.

TPP met the criteria for classification as Skin Sens 1A in the one available LLNA, having an EC3 value of 1.4; it is thus regarded as a strong sensitiser in accordance with the GHS system for harmonised classification and labelling, and as an extreme sensitiser in accordance with the scheme developed by the EU Expert Group on skin sensitisation (Basketter *et al.* (2005)). Based on this end-point, a qualitative judgement can be made that TPP is in the high-hazard category in terms of the RMMs and OCs that should be considered (ECHA (2012)). As the eMSCA has reservations about a DNEL for skin sensitisation giving a safe level of exposure, a qualitative approach alone will be followed.

Inhalation route of exposure (workers)

Local effects on the respiratory tract upon long-term exposure have not been evaluated. However, the eMSCA notes that no adverse effects on the respiratory tract were reported in the acute inhalation toxicity study (the only study available via the inhalation route).

Long-term exposures – systemic effects

The eMSCA has derived its own DNELs for dermal and inhalation exposure. No sub-chronic or chronic studies are available. Information on repeated-dose systemic effects is available from an oral, combined repeated-dose toxicity / reproductive toxicity screen study (OECD 422) in rats. A NOAEL of 5 mg/kg/d for male and female systemic toxicity was identified from this study, which differs from that identified by the registrants (15 mg/kg/d). This was lower than the reproductive (≥ 40 mg/kg/d) and developmental (15 mg/kg/d) NOAELs identified from the same study and the same as the NOAEL for F1 adult systemic toxicity, and will thus be used to calculate the DNELs.

No toxicokinetic data are available on the oral, dermal and inhalation absorption of TPP. Based on toxicology data, physico-chemical information and the known toxicokinetics of the main hydrolysis product, phenol, the registrants assumed an oral absorption of 100%, a dermal absorption of 50% and an inhalation absorption of 100%. In the absence of specific information on TPP, the eMSCA will apply the default (worst-case) values, as given in the guidance (ECHA (2010)). The eMSCA notes that the registrants are currently in the process of conducting a dermal absorption study. The results of this can be used to refine the DNEL in the future.

Given that the dermal absorption is unclear, the DNELs have been calculated using 100% (worst case scenario), 50% (registrants proposal) and 10% (lowest value which may be applicable, based on various guidance documents).

Dermal route of exposure (workers)

(i) Based on 100% dermal absorption (worst case scenario)

Route-to-route extrapolation

In the absence of a repeated-dose dermal toxicity study, the dermal NOAEL was extrapolated from the oral NOAEL. On the assumption that dermal absorption will not be higher than oral absorption, no default factor was introduced for the oral-to-dermal extrapolation, although it is recognised that assuming equivalent oral and dermal absorption might give a conservative value (based on TPP's log Kow of 6.6). It is also assumed that human dermal absorption is the same as rat dermal absorption.

Corrected Dermal NOAEL = 5 mg/kg/day x (1/1) x (1/1) = 5 mg/kg/day

Assessment factors

To convert the rat dermal NOAEL to the human equivalent, the following AFs have been applied.

- Interspecies differences = 4 for allometric scaling and 2.5 for remaining differences (total 10 - default).
- Intraspecies differences = 5 for workers (default). There was no indication from the available data that the young are more sensitive to the toxic effects of TPP; therefore, a factor of 10 is considered to be sufficiently protective for pregnant women.
- Duration of exposure = 6 for sub-acute to chronic. The NOAEL was identified from males exposed for 28 days and females exposed for 70 days. Extrapolation from sub-acute to chronic is not considered to be overly conservative, considering the progressive nature of the TPP toxicity and the occurrence of effects in males at the LOAEL after 28 days of administration.
- Dose-response relationship = 1. A NOAEL was available, the effects at the LOAEL were not severe, the dose-spacing was close, and the study was of adequate quality.

- Quality of whole database = 2. The only study submitted to inform on repeated-dose toxicity and reproductive toxicity was a combined repeated-dose toxicity / reproductive screening test. It is not possible to judge the consistency of the results from this one study. However, the study was modern, conducted to GLP and was modified to enhance the standard OECD 422 protocol. An additional factor of 2 for the quality of the database was therefore added.

Total Assessment Factor = 600.

Overall, the worker $DNEL_{Dermal\ -\ Long\text{-}Term\ Systemic}$ = 5 mg/kg/d / 600 = 0.0083 mg/kg/day

(ii) *Based on 50% dermal absorption*

Although the dermal absorption of TPP is not known, it is reasonable to assume that it will be less than 100%, based on the information available. Therefore, the eMSCA has also calculated the dermal DNEL based on 50% absorption (as proposed by the registrants).

Route-to-route extrapolation

Corrected Dermal NOAEL = 5 mg/kg/day x $ABS_{oral\text{-}rat}$ / $ABS_{dermal\text{-}rat}$ x $ABS_{dermal\text{-}rat}$ / $ABS_{dermal\text{-}human}$

= 5 mg/kg/day x (100%/50%) x (1/1)

= 10 mg/kg/day

Assessment factors

To convert the rat dermal NOAEL to the human equivalent, the following AFs have been applied.

- Interspecies differences = 4 for allometric scaling and 2.5 for remaining differences (total 10 - default).
- Intraspecies differences = 5 for workers (default).
- Duration of exposure = 6 for sub-acute to chronic.
- Dose-response relationship = 1.
- Quality of whole database = 2.

Total Assessment Factor = 600.

Overall, the worker $DNEL_{Dermal\ -\ Long\text{-}Term\ Systemic}$ = 10 mg/kg/d / 600 = 0.016 mg/kg/day

(iii) Based on 10% dermal absorption

Corrected Dermal NOAEL = 5 mg/kg/day x $ABS_{oral\text{-}rat}$ / $ABS_{dermal\text{-}rat}$ x $ABS_{dermal\text{-}rat}$ / $ABS_{dermal\text{-}human}$

= 5 mg/kg/day x (100%/10%) x (1/1)

= 50 mg/kg/day

Assessment factors

To convert the rat dermal NOAEL to the human equivalent, the following AFs have been applied.

- Interspecies differences = 4 for allometric scaling and 2.5 for remaining differences (total 10 - default).
- Intraspecies differences = 5 for workers (default).
- Duration of exposure = 6 for sub-acute to chronic.
- Dose-response relationship = 1.
- Quality of whole database = 2.

Total Assessment Factor = 600.

Overall, the worker $DNEL_{Dermal\ -\ Long\text{-}Term\ Systemic}$ = 50 mg/kg/d / 600 = 0.083 mg/kg/day

Inhalation route of exposure (workers)

Route-to-route extrapolation

In the absence of a repeated-dose inhalation toxicity study, the inhalation NOAEL was extrapolated from the oral NOAEL. The default (worst-case) oral absorption values of 50% for oral and 100% for inhalation were assumed.

Corrected inhalation NOAEC = 5 mg/kg/d x (1/0.38m^3/kg/8 hr) x (50/100) x 0.67

= 4.41 mg/m^3 (8 hr)

Assessment factors

The rationale for choosing the AFs to convert the rat inhalation NOAEC to a human equivalent is the same as for the dermal route of exposure for workers, except that a factor for allometric scaling is not required. In summary:

- Interspecies differences = 1 for allometric scaling and 2.5 for remaining differences (total 2.5 - default)
- Intraspecies differences = 5 for workers (default)
- Duration of exposure = 6 for sub-acute to chronic
- Dose-response relationship = 1
- Quality of whole database = 2

Total Assessment Factor = 150.

Overall, the worker $DNEL_{Inhal\ -\ Long\text{-}Term\ Systemic}$ = 4.41 / 150 = 0.029 mg/m^3/8 hrs.

DN(M)ELs for consumers: discussion

Acute exposures – systemic effects

No evaluation of $DNEL_{acute}$ for systemic effects has been performed. The long-term DNELs are assumed to be sufficiently protective.

Acute and long-term exposures – local effects

Dermal route of exposure (consumers)

The following general approach to the characterisation of dose-response relationships from LLNA data is recommended (ECHA (2010)):

1. a qualitative approach (by the use of potency categorisation) to define the risk management measures (RMMs) and operational conditions (OCs); and,
2. setting a DNEL (if possible) to judge the remaining likelihood of risks after these RMMs and OCs have been implemented.

TPP met the criteria for classification as Skin Sens 1A in the one available LLNA, having an EC3 value of 1.4; it is thus regarded as a strong sensitiser in accordance with the GHS system for harmonised classification and labelling, and as an extreme sensitiser in accordance with the scheme developed by the EU Expert Group on skin sensitisation (Basketter *et al.* (2005)). Based on this end-point, a qualitative judgement can be made that TPP is in the high hazard category in terms of the RMMs and OCs that should be considered (ECHA (2012)). As the eMSCA has reservations about a DNEL for skin sensitisation giving a safe level of exposure, a qualitative approach alone will be followed.

Inhalation route of exposure (consumers)

Local effects on the respiratory tract upon long-term exposure have not been evaluated.

Long-term exposures – systemic effects

The eMSCA has derived DNELs for oral, dermal and inhalation exposure. As noted in the discussion on worker DNELs, a NOAEL of 5 mg/kg/d for male and female systemic toxicity was identified from the oral OECD 422 study in rats, which differs from that identified by the registrants (15 mg/kg/d). In the absence of specific toxicokinetic information on TPP, the eMSCA will apply the default (worst-case) values, as given in the guidance (ECHA (2010)).

Oral route of exposure (consumers)

Modification of starting point

There is no information on the oral absorption of TPP in either rats or humans; an oral absorption value of 100% will therefore be assumed for both species. No modification of the starting point (5 mg/kg/d) is needed.

Assessment factors

The following AFs were applied to convert the rat oral NOAEL to a human equivalent.

- Interspecies differences = 4 for allometric scaling and 2.5 for remaining differences (total 10 - default).

- Intraspecies differences = 10 for consumers (default). There was no indication from the available data that the young are more sensitive to the toxic effects of TPP; therefore, a factor of 10 is considered to be sufficiently protective for young children and pregnant women.
- Duration of exposure = 6 for sub-acute to chronic. The NOAEL was identified from males exposed for 28 days and females exposed for 70 days. Extrapolation from sub-acute to chronic is not considered to be overly conservative, considering the progressive nature of the TPP toxicity and the occurrence of effects in males at the LOAEL after 28 days of administration.
- Dose-response relationship = 1. A NOAEL was available, the effects at the LOAEL were not severe, the dose-spacing was close, and the study was of adequate quality.
- Quality of whole database = 2. The only study submitted to inform on repeated-dose toxicity and reproductive toxicity was a combined repeated-dose toxicity / reproductive screening test. It is not possible to judge the consistency of the results from this one study. However, the study was modern, conducted to GLP and was modified to enhance the standard OECD 422 protocol. An additional factor of 2 for the quality of the database will therefore be applied.

Total AF = 1200

Overall, the consumer $DNEL_{long\text{-}term\ oral\ systemic}$ = 5 mg/kg/d / 1200 = 0.004 mg/kg/d

Dermal route of exposure (consumers)

Route-to-route extrapolation

In the absence of a repeated-dose dermal toxicity study, the dermal NOAEL was extrapolated from the oral NOAEL. In the absence of any evidence to the contrary, and based on the guidance, an equivalent oral and dermal absorption was assumed. It is also assumed that human dermal absorption is the same as rat dermal absorption. As for workers, DNELs have been calculated assuming 100%, 50% and 10%.

(i) <u>Assuming 100% dermal absorption</u>

Corrected Dermal NOAEL = 5 mg/kg/day x (1/1) x (1/1) = 5 mg/kg/day

Assessment factors

The rationale for choosing the AFs is the same as for the oral route of exposure for consumers. In summary:

- Interspecies differences = 4 for allometric scaling and 2.5 for remaining differences (total 10 - default).
- Intraspecies differences = 10 for consumers (default).
- Duration of exposure = 6 for sub-acute to chronic.
- Dose-response relationship = 1.
- Quality of whole database = 2.

Total AF = 1200

Overall, the consumer $DNEL_{long\text{-}term\ dermal\ systemic}$ = 5 mg/kg/d / 1200 = 0.004 mg/kg/d

(ii) Assuming 50% dermal absorption

Corrected Dermal NOAEL = 5 mg/kg/day x (100%/50%) x (1/1) = 10 mg/kg/day

Assessment factors

The rationale for choosing the AFs is the same as for the oral route of exposure for consumers. In summary:

- Interspecies differences = 4 for allometric scaling and 2.5 for remaining differences (total 10 - default).
- Intraspecies differences = 10 for consumers (default).
- Duration of exposure = 6 for sub-acute to chronic.
- Dose-response relationship = 1.
- Quality of whole database = 2.

Total AF = 1200

Overall, the consumer $DNEL_{long\text{-}term\ dermal\ systemic}$ = 10 mg/kg/d / 1200 = 0.008 mg/kg/d

(iii) Assuming 10% dermal absorption

Corrected Dermal NOAEL = 5 mg/kg/day x (100%/10%) x (1/1) = 50 mg/kg/day

Assessment factors

The rationale for choosing the AFs is the same as for the oral route of exposure for consumers. In summary:

- Interspecies differences = 4 for allometric scaling and 2.5 for remaining differences (total 10 - default).
- Intraspecies differences = 10 for consumers (default).
- Duration of exposure = 6 for sub-acute to chronic.
- Dose-response relationship = 1.
- Quality of whole database = 2.

Total AF = 1200

Overall, the consumer $DNEL_{long\text{-}term\ dermal\ systemic}$ = 50 mg/kg/d / 1200 = 0.042 mg/kg/d

Inhalation route of exposure (consumers)

Route-to-route extrapolation

In the absence of a repeated-dose inhalation toxicity study, the inhalation NOAEL was extrapolated from the oral NOAEL. The default (worst-case) oral absorption values of 50% for oral and 100% for inhalation will be assumed.

Corrected inhalation NOAEC = 5 mg/kg/d x (1/1.15m^3/kg/24 hr) x (50/100)

= 2.17 mg/m^3/24 hr

Assessment factors

The rationale for choosing the AFs is the same as for the oral route of exposure for consumers, except that a factor for allometric scaling is not required. In summary:

- Interspecies differences = 1 for allometric scaling and 2.5 for remaining differences (total 2.5 - default).
- Intraspecies differences = 10 for consumers (default).
- Duration of exposure = 6 for sub-acute to chronic.
- Dose-response relationship = 1.
- Quality of whole database = 2.

Total AF = 300

Overall, the consumer $DNEL_{long\text{-}term\ inhalation\ systemic}$ = 2.17 mg/kg/24 hr / 300 = 0.007 mg/m^3/24 hr

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

No specific data on toxico-kinetics is available for TPP. The results of oral toxicity tests indicate that TPP is readily absorbed by the oral route, and thus an oral absorption of 100% is assumed by the registrants. Likewise, an inhalation absorption of 100% is also assumed. The registrants arbitrarily decided on a dermal absorption of 50%.

There is no information on the effects of a single exposure to TPP in humans. In animals, it exhibited toxicity by the oral route, with an LD_{50} of 1590 mg/kg. TPP was not acutely toxic by the dermal or inhalation routes of exposure when tested at doses or concentrations greater than the limit dose / concentration.

The irritancy of TPP has been tested in animals, indicating that it is slightly irritating to the skin and irritating to the eyes. There were no indications of corrosivity. The skin sensitisation potential of TPP has been investigated in a LLNA, in which a positive response was achieved with an EC3 value of 1.4%; thus, the substance should be regarded as a strong sensitiser. Supportive information was provided by a guinea-pig maximisation test and case reports of skin sensitisation in humans. There is no information on the potential of TPP to be a respiratory sensitiser.

There is no information available on the effects of repeated exposure in humans. In animals, TPP has been investigated in a combined repeated-dose toxicity and reproduction screening test (OECD 422, with modifications); some additional information was provided by a range-finding study. Severe toxicity, particularly evident as neurotoxicity, occurred in both sexes and was progressive. A NOAEL-28 days of 5 mg/kg/d was identified. A longer-term study was not available. However, since TPP meets the criteria for classification for repeated-dose toxicity and the NOAEL-28 days can be extrapolated to a longer-term duration of exposure, a sub-chronic or chronic study is not required in this substance evaluation

The mutagenic profile of TPP has been investigated *in vitro* in bacteria and in a micronucleus test conducted on human lymphocytes, in an *in vivo* micronucleus assay. All of these tests were negative, and there is no concern for genotoxicity.

There is no information on the carcinogenic potential of TPP in humans or animals. No effects of concern for carcinogenicity (hyperplasia, pre-neoplastic lesions) were observed in the one repeated-dose toxicity study and the available genotoxicity data, does not indicate that TPP is mutagenic.

The reproductive toxicity of TPP has been investigated in animals in a combined repeated-dose toxicity / reproductive toxicity screen (OECD 422 with modifications). Reproduction parameters were unaffected and there were no reported variations, malformations or anomalies, but offspring toxicity was evident at 40 mg/kg/d (reductions in survival indices, numbers of live pups/litter and pup body weights, increased pup mortality during lactation). However, these effects occurred only in the high-dose group and in conjunction with severe maternal toxicity, including severe ataxia; at doses at which maternal toxicity did not occur, there were no developmental or offspring effects. Only slight toxicity was evident in the F1 offspring that were raised to adulthood and occurred to a similar level to that observed in F0 animals that began their exposure as animals. From the information available at the time of the substance evaluation, there was therefore no evidence of a specific effect on reproduction or development, or that offspring exposed prenatally and during lactation were more sensitive to TPP toxicity than animals exposed only from adulthood. The following NOAELs were identified: 5 mg/kg/d for adult systemic toxicity; ≥ 40 mg/kg/d for fertility impairment; 15 mg/kg/d for offspring toxicity.

An initial screen of the results of the OECD 422 study raised a concern for endocrine disruption (effects on adrenal glands, testes, brain). These effects consisted of organ weight changes without evidence of (histo)pathological changes or functional disturbances. Furthermore, the increase in relative brain weight could be attributed to the decrease in terminal body weight. The weight changes in the adrenal glands occurred only in F0 males and were not statistically significant. Therefore, the only adverse effects that potentially indicated endocrine disruption were slight reductions in weights of the epididymides and prostate (at PND 21 only) in F1 males. Overall, it was concluded from the available information that these effects were indicative of general toxicity and not endocrine disruption.

TPP is listed on Annex VI of CLP with the following human health classification and labelling:

Eye Irrit. 2 – H319 (Causes serious eye irritation (C ≥ 5%))

Skin Irrit. 2 – H315 (Causes skin irritation (C ≥ 5%))

In addition to these, the registrant(s) self-classify as:

Acute Tox. 4 – H302 (Harmful if swallowed)

Skin Sens. 1 – H317 (May cause an allergic skin reaction)

STOT-RE 2 – H373 (May cause damage to organs (nervous system) through prolonged or repeated exposure)

The eMSCA agrees with the self classifications for Acute Tox 4 and STOT-RE 2; however the available data indicate that TPP meets the classification criteria for Skin Sens 1A and this more severe classification should be applied.

It is therefore the recommendation of this evaluation that a CLH proposal is taken forward to amend the harmonised classification for TPP.

7.12. Assessment of endocrine disrupting (ED) properties

7.12.1. Endocrine disruption - Human health

A combined repeated-dose toxicity with reproduction/developmental toxicity screening study (OECD 422) revealed effects potentially related to endocrine disruption (effects on adrenal glands, testes, brain). The end-points potentially sensitive to endocrine disruption (OECD (2012)) and included in the OECD 422 study design are summarised in the table below. These were evaluated to determine if further information was required to clarify the concern.

Table 26. Effects of TPP on endocrine end-points following oral administration

Method	Results	Remarks	Reference
Rat (Sprague-Dawley) male/female Combined repeated dose and reproduction / developmental screening (oral: gavage) 0, 5, 15 and 40 mg/kg/day: *- 10/sex/dose for 2 weeks of pre-breed exposure, 2 weeks of mating, 3 weeks each of gestation and lactation (F0 females)* *- direct dosing of F1 offspring from weaning for at least 7 weeks* 0 and 40 mg/kg/d: *- 5 F0 males/group designated as recovery animals (2 weeks without dosing after the F0 male dosing period was completed (28 days)*	***28-day exposure females & F0 adults*** Ovary, uterus/cervix, vagina: no changes in absolute or relative weights & no gross or histopathology findings (28-day & PND 21). Epididymides, prostate and seminal vesicles with coagulating glands (28 days): no changes in absolute or relative weights of seminal vesicles with coagulating glands. Paired epididymides weight relative to body weight significantly increased by 14% at 40 mg/kg/d; no dose-related absolute change or relative to brain weight. Absolute prostate weights decreased by 26%, relative to body weight by 19% & relative to brain weight by 19% at 40 mg/kg/d but none statistically significant when analysed by regression to test for overall treatment group differences. One male at 40 mg/kg/d had a seminal vesicle reduced in size. No gross or histopathology findings. Testes (28 days): no statistically-significant changes in absolute or relative weights. No histopathology findings. Thyroids: females (28 days) – ultimobranchial cysts in 1 female at 0 mg/kg/d & 4 at 40 mg/kg/d; PND 21 – ultimobranchial cysts in 3 females at 0 mg/kg/d & 2 at 40 mg/kg/d. No findings in males. No gross or histopathological changes in the liver of F0 males or females to suggest involvement of the thyroid-pituitary axis. Adrenal glands: females – no changes in adrenal gland absolute or relative weights or histopathology findings (28 days & PND 21). Males – dose-related trend towards higher absolute weight but not statistically significant (increases of < 1%, 9%, 13% at 5, 15, 40 mg/kg/d); increase in weight (17%) relative to body weight only at 40 mg/kg/d, not statistically significant; dose-related trend towards higher weight relative to brain weight (5%, 10%, 15% at 5, 15, 40 mg/kg/d) but not statistically significant. No gross or histopathology changes in males. Brain: no changes in male absolute or relative brain weight. No gross or histopathology findings (males).	1 (reliable without restriction) **Test material (EC name): triphenyl phosphite**	Unpublished (2004)

Method	Results	Remarks	Reference
- 5 females/group dosed for 28 days *- 5 females/group dosed for 28-day followed by 2-week recovery period.* Equivalent or similar to OECD Guideline 422	Female brain weight relative to body weight significantly increased by 27% at 40 mg/kg/d but absolute weight unaffected (PND 21; no changes at 28 days). Changes in time to mating, male fertility, female fertility, dystocia, gestation length, number of implantations: no statistically-significant effects. ***F1 offspring:*** Number of live births and post-implantation loss, litter size, viability index, litter/pup weight, pup survival index, abnormalities in pup development: live pups/litter reduced at 40 mg/kg/d. No statistically significant effect on number of total implantation sites per litter and the number of total and live pups per litter at birth, nor on the number of dead pups at birth. Post-implantation loss per litter was increased with TPP but not in a dose-related manner. Pup survival during lactation reduced at 40 mg/kg/d, secondary to maternal toxicity. No abnormalities in pup development. Necropsy was not performed on F1 pups at 40 mg/kg/d, owing to excessive maternal and offspring toxicity in this group. Anogenital distance: no statistically-significant change in males or females of any group. Oestrus cyclicity: equivalent across all groups. Age at vaginal patency: equivalent across all dose groups. Age at preputial separation: no statistically-significant changes. Nipple and areolae retention: no male pups with nipples on PND 11-13. Number of areolae per male pup and number of pups with one or more areolae on PND 11-13 were equivalent across groups. Genital abnormalities: none recorded. Weights of female reproductive organs: no changes in uterus with cervix and vagina weight or paired ovaries on PND 21 or 7 weeks post-weaning. Weights of male reproductive organs: PND 21 – no effects on absolute or relative values of paired testes. Absolute paired epididymides weights significantly reduced at 5 and 15 mg/kg/d (by 12% and 13%, respectively, compared with controls); also reduced relative to body weight (by 14%) and brain weight (by 13%) at 15 mg/kg/d. Prostate weight not determined at PND 21. 7 weeks post-weaning – no change in absolute paired testes or paired epididymides weights. Absolute prostate weight significantly decreased (by 22%) at 15 mg/kg/d. Prostate weight relative to body		

Method	Results	Remarks	Reference
	weight was significantly reduced at 5 and 15 mg/kg/d (23% and 26%, respectively). Gross necropsy & histopathology of female reproductive organs: no treatment-related gross or histopathology findings. Gross necropsy & histopathology of male reproductive organs: 1 male at 5 mg/kg/d with testes reduced in size bilaterally (PND 21), 1 male at 15 mg/kg/d with epididymides and testes reduced in size bilaterally (7 weeks post-weaning). Sperm parameters: no differences between groups for percent motile sperm or percent progressively motile sperm. No differences between 0 & 15 mg/kg/d groups for epididymal sperm concentration & testicular spermatid homogenisation-resistant spermatid head count, daily sperm production, efficiency of daily sperm production or percent abnormal sperm. Sex ratio: no statistically-significant difference in any group (% of males per litter 45.7, 41.0, 42.0, 39.3 at 0, 5, 15, 40 mg/kg/d). Thyroid: in males, no histopathology findings. Two females at 15 mg/kg/d had ultimobranchial cysts. No liver weight increases or hepatocellular hypertrophy after 7 weeks post-weaning to suggest involvement of the thyroid-pituitary axis (males & females). Brain weight: no change in males or females. Adrenal glands: no change in paired weights for males or females after 7 weeks of post-weaning exposure. Pituitary: not investigated.		

The reproduction/developmental screening test OECD 422 is included in Level 4 of the OECD conceptual framework for the testing and assessment of endocrine disruptors (OECD (2012)) as a supplemental test. It is regarded as providing limited but useful information on the interaction with endocrine systems through effects on reproduction (gestation, gestation length, dystocia, implantation losses), genital malformations in offspring, marked feminised anogenital distance in males, changes in histopathology of sex organs or effects on the thyroid gland. When following the standard protocol, the detection of endocrine effects in female reproductive organs is made more difficult because the same level of investigation is not possible in pregnant animals; however, this deficit was abrogated in the TPP study because of the inclusion of non-pregnant, 28-day exposure groups and the continuation of the F1 generation to adulthood.

In addition to gross and histopathological investigations of the male and female reproductive organs and brain and adrenal glands (amongst other organs), the study protocol included an examination of anogenital distance (PND 0), retained nipples and areolae (PND 1-13), oestrus cyclicity (during the last three weeks of the post-wean period), acquisition of vaginal patency (at weaning) and acquisition of preputial separation (part-way through the post-weaning exposure). F1 male andrology was also investigated after seven weeks of post-weaning exposure, comprising examination of one cauda epididymis from each male and seminal fluid for sperm number, motility and morphology.

In this study, the findings of relevance to a potential endocrine disruption mode of action for TPP were some changes in organ weights, a reduction in the number of live pups/litter and reduced survival during lactation at 40 mg/kg/d. As discussed in section 5.9.3, the latter two effects occurred in conjunction with severe maternal toxicity and so are not regarded as specific effects on development; no other reproductive or developmental parameters were affected.

The following changes in organ weights were noted in males:

- paired epididymides relative to body weight increased in F0 males at 40 mg/kg/d but reduced in F1 (absolute and relative to body and brain weight) at PND 21 (15 mg/kg/d), with no differences between groups in F1 adults;
- absolute and relative to body weight prostate weight decreased in F0 males at 40 mg/kg/d (not statistically significant) and F1 adults at 5 (relative to body weight only) and 15 mg/kg/d;
- non-statistically significant but dose-related increase in adrenal gland absolute weights and relative to brain weight, increase relative to body weight only at 40 mg/kg/d in F0 males.

The following changes in organ weights were noted in females:

- brain weight relative to body weight increased at 40 mg/kg/d (F0), no change in absolute weight.

These changes in organ weights were not associated with any gross or histopathological changes. Ultimobranchial cysts were recorded in the thyroid of a number of 28-day, F0 and F1 females, but a higher incidence in F0 control females than in the 40 mg/kg/d group indicated that they were not likely to be treatment-related.

The increase in brain weight relative to body weight but without a change in absolute weight in F0 females reflected the reduced body weight in these animals; it is therefore concluded that administration of TPP did not have an adverse effect on the brain in the investigations undertaken for this study. Similarly, the increase in paired epididymides weights in F0 adults relative to body weight was the result of the decreased terminal body weight at 40 mg/kg/d. The reductions in absolute paired epididymides in F1 weanlings at 5 and 15 mg/kg/d and relative to body weight and brain weight at 15 mg/kg/d did appear to be treatment-related, although these changes were not apparent in F1 adults. Prostate weights were reduced only at 40 mg/kg/d in absolute terms and relative to body and brain weight in F0 males, but without statistical significance or a dose-response relationship. The reductions in prostate weight in F1 adults were statistically significant and are regarded as treatment related, although it is noted that a slight increase in terminal body weights at 5 and 15 mg/kg/d affected the prostate:body weight ratios. Changes in the weights of the adrenal glands were observed only in F0 males and without statistical significance; the weights in all females and F1 adults were equivalent across groups.

In summary, treatment-related changes in organ weights were recorded in the epididymides of F1 weanlings (decrease), the prostate of F0 males (although not statistically significant and in conjunction with general toxicity) and F1 adults (decrease), adrenal glands of F0 males (increase, not statistically significant) and kidneys of F0 females (decrease). Apart from the prostate, there was no consistency in the findings between generations, although it is recognised that the high-dose group F1 offspring were not investigated by necropsy. Notwithstanding, it would normally be expected that offspring exposed prenatally would be more sensitive to endocrine-disrupting effects; in this study, such a pattern of findings was only apparent in relation to the epididymides and prostate. These effects were relatively slight (up to approximately 22%) reductions in the organ weights at 5 and 15 mg/kg/d; it is further noted that the effects on the epididymides were apparent only on PND 21, not after seven weeks of post-weaning exposure. Other indications of toxicity that occurred in these animals were some changes in blood clinical

chemistry and haematology parameters. More importantly, TPP exposure did not induce any functional effects on reproduction, sperm parameters, nipple/areolae retention, oestrus cyclicity, anogenital distance, preputial separation, vaginal patency, thyroid or pathology of reproductive organs. As discussed in section 5.9.3, there were no developmental effects in the absence of maternal toxicity. It is also possible for endocrine disruptors to induce neurotoxicity (IPCS (International Programme on Chemical Safety) (2002)), but pre- and post-natal exposure to TPP revealed no such effects in F1 animals in the tests conducted. It is therefore concluded that the observed changes in organ weights were a sensitive indicator of general toxicity, not of endocrine disrupting properties.

The available evidence indicates that TPP is not an endocrine disruptor in relation to human health, because it did not produce clear effects on the endocrine system or endocrine-mediated functions. The concern has been clarified and no further information is requested.

7.12.2. Endocrine disruption – Environment

One of the key environmental grounds for concern taken from the CoRAP justification document related to the potential for TPP, or some of its phenolic hydrolysis products, to possess estrogenic or endocrine disruptor (ED) activity. Human health screening studies have previously reported affected relative paired testes, adrenal glands and brain weights).

No ED toxicity data are available on the effects of TPP itself on aquatic and terrestrial organisms. There are no acute or chronic (e.g. reproductive) ecotoxicity data on TPP which could indicate a potential for endocrine disruption. Reference has therefore been made to the available information on TPP from the relevant human health assessment (Section 7.13.1) and from other available information on phenol (e.g. European Chemicals Bureau, Risk Assessment Report (2006)).

Section 7.13.1 discusses a combined repeated-dose toxicity with reproduction/ developmental toxicity screening study on TPP (OECD 422). One of the grounds for concern for TPP was endocrine disruption, based on effects on adrenal glands, testes, brain in this study. However, the conclusion of the eMSCA is that the available evidence does not indicate that TPP is an endocrine disruptor in relation to human health, since it did not produce clear effects on the endocrine system or endocrine-mediated functions. The ED concern in relation to human health has been clarified and no further information is requested.

The overall indicators from mammalian toxicity data on TPP therefore do not predict significant endocrine disrupting activity. Given the lack of evidence for endocrine disruption in relation to human health and the lack of other ecotoxicological data on TPP, it is considered that TPP does not pose an ED hazard in aquatic and terrestrial organisms.

Since TPP also hydrolyses and biotically degrades rapidly to phenol and phosphorous acid (ref: Section 7.7) there is considered to be a low potential for significant environmental exposure directly to TPP. However, it is appropriate to also consider whether there is any ED information on the primary degradant, phenol. The detailed ECB Risk Assessment Report (2006) on phenol has been consulted and this does not raise any concerns regarding the environmental ED potential of phenol. Additionally, there was no evidence of endocrine disruption from phenol in the mammalian toxicity studies evaluated in this ECB report.

A brief examination of other publically available information on phenol also does not highlight any concerns for endocrine-mediated reproductive or developmental effects in mammalian or other aquatic or terrestrial organisms. Phosphorous acid is an inorganic and ionic substance and is not expected to persist under normal environmental conditions; it is not envisaged to show any ED activity.

In conclusion, based on criteria for determining ED potential for the environment, there are no indications so far from available information on TPP or its main degradation products, phenol and phosphorous acid, that would lead to concerns or further testing of ED potential in the environment.

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

Overall the human health (7.13.1) and environmental (7.13.2) ED assessments for TPP and its degradation products do not indicate any substantive ED hazard to mammalian (human) or other aquatic or terrestrial life. Given this lack of activity as well as the rapid transformation of TPP in environmental systems and predicted low levels of exposure to TPP itself, the risk from ED activity of TPP is also considered to be minimal. The eMSCA therefore concludes that further ED testing on TPP is not warranted.

7.13. PBT and vPvB assessment

Assessment of PBT/vPvB properties – Comparison with the criteria of Annex XIII

i) Persistence (P/vP) assessment

The low water solubility and anticipated rapid hydrolysis of TPP has hindered earlier attempts to experimentally quantify its environmental persistence. The lead Registrant for TPP has updated their dossier in relation to key studies relating to its abiotic and biotic degradation. The most recently submitted hydrolysis (Unpublished, 2017c) and ready biodegradation tests (Unpublished, 2015) are evaluated above in Sections 7.7.1.1 (iii) and 7.7.2.1.2 (ii) respectively. These studies are considered reliable and indicate rapid degradation of any solubilised TPP that is available for hydrolytic or biotic reactions.

Based on oxygen consumption in a closed-bottle test, the OECD 301D biodegradation study (Unpublished, 2015) has shown 84% degradation of TPP at day-28 with over 60% biodegradation achieved in a period of 6 days immediately following the attainment of 10% biodegradation. Hence, triphenyl phosphite can be considered as being 'readily biodegradable' under the conditions of this study. The hydrolysis study (Unpublished, 2017c) is also consistent with the expectation that TPP rapidly hydrolyzes to phenol and phosphorous acid. Information from other sources, e.g. the EU Risk Assessment Report for phenol (European Chemicals Bureau (2006)), concludes that the hydrolysis products of TPP, phenol and phosphorous acid, are then also not persistent.

The reliable hydrolysis and screening ready biodegradation studies demonstrates that TPP is not persistent in the environment and would not meet the REACH Annex XIII 'P' criteria in various environmental compartments which range from half-lives in fresh or estuarine water of >40 days, to >180 days in marine sediment. Degradation of TPP would also not meet the even longer half-life criteria for 'vP' and overall further degradation simulation testing on TPP itself is not considered to be warranted. The hydrolysis products of TPP (phenol and phosphorous acid) also do not meet the criteria for P or vP.

2) Bioaccumulation (B/vB) assessment

The estimated log K_{ow} for TPP is 6.62, which would normally indicate a potential for bioaccumulation. According to the Registrant, an experimental bioconcentration factor (BCF) cannot be experimentally measured for TPP owing to its rapid hydrolysis. The BCF modelling estimates for TPP (using BCFBAF v3.00 model) are very low but are also of limited utility given their wide range and the fact that hydrolysis and biotic degradation is not considered in the models (see Section 7.7.4). Given this rapid degradation, the bioaccumulation potential of the hydrolysis products, phenol and phosphorous acid, were also considered.

The experimental log Kow of phenol (the primary hydrolysis product) is 1.47 and its BCF is 17.5 L/Kg (European Chemicals Bureau (2006)). Phenol therefore does not meet the REACH Annex XIII criterion for 'B' (bioaccumulative, i.e. a BCF in aquatic species of>2000)

or 'vB' (very bioaccumulative, i.e. a BCF in aquatic species of>5000). As such, it is concluded that TPP does not itself meet the criteria for B or vB. *This information supports the conclusion that neither TPP nor its hydrolysis products are expected to bioaccumulate and do not meet the criteria for B or vB.*

3) Toxicity (T) assessment

The information evaluated in this report indicates that TPP meets the criteria for classification for mammalian repeated-dose toxicity (STOT-RE 2 – H373) see Section 4.1.1. Based on the latter classification, TPP thus meets the 'T' criterion in accordance with Annex XIII of REACH.

There are no direct experimental data on the aquatic toxicity of TPP since it cannot be reliably tested due to its low water solubility and rapid hydrolysis. It is unlikely to be toxic to aquatic organisms due to its rapid transformation to non-classified substances.

4) Summary and overall conclusions on PBT and vPvB properties

TPP is determined to be Toxic (T) based on its classification as STOT-RE 2. However, as TPP does not meet the criteria for P/vP or B/vB, it is not considered to be a PBT or vPvB substance.

7.14. Exposure assessment

7.14.1. Exposure related to human health

In March 2013, when this evaluation was initiated, ECHA identified eight registrants for this substance with an aggregated tonnage of 1,000 – 10,000 tpa. This includes tonnage used as an intermediate under strictly controlled conditions (SCC). By January 2019, when the final evaluation report was prepared, a further six companies had registered (of these, two are members of a separate joint submission) and two of the original registrants declared their registrations inactive. The aggregated tonnage remained in the 1,000 – 10,000 tpa band. This evaluation is based on registrations as they stood in January 2019.

7.12.1.1 Observations made during the initial evaluation

The initial evaluation determined that not enough information had been provided in CSRs to enable the eMSCA to run the ECETOC TRA (v2) exposure model with any degree of confidence and replicate the modelling estimates produced by the registrant(s), nor to allow a decision to be made regarding any modifiers used in the registrants' assessment. Requests for further information on human exposure were therefore included in the decision issued on 2 December 2015. For workers, additional details were required to help the eMSCA understand the tasks covered by each exposure scenario, also the operating conditions (OCs) and risk management measures (RMMs) that were applicable to each task. It was not clear how OCs and RMMs had been taken into account in the exposure calculations and insufficient information was provided about the types of gloves (materials, thicknesses and breakthrough times) and types of RPE that should be used where these measures are necessary. The eMSCA also asked the registrants to provide a scientific justification for the RMM efficiency tiers that were being used in the exposure calculations and for a generic statement be included in the CSR to indicate that training should be given on the correct use of all control measures, including PPE.

Much of this information is still missing from the latest updates of registrations.

Requests were also made for information on consumer exposure and combined workplace/consumer exposure. New information obtained by the PSRC indicates that TPP and mixtures containing TPP are not supplied to consumers (or for use by professionals) and this is reflected in updates.

Note to registrants: To ensure accurate information is available to authorities in relation to the uses and the conditions of use that are supported, all registrants should ensure that they update their CSRs promptly when they receive new information. The comments provided by the eMSCA in this report about the use and exposure information presented in registrations constitute new information. All registrants, including those whose registrations were not included in this evaluation, should ensure (subject to tonnage requirements) that an exposure scenario is available for each of the uses that they cover in their registration and should take account of the findings from this substance evaluation in their own chemical safety assessments.

The final exposure request concerned information on use under SCC. One registrant supplying tonnage for use as an intermediate under SCC still has not either confirmed, or stated that they have received confirmation from their downstream user, that use of TPP takes place under SCC.

In the light of the sparse information provided by registrants and in order to progress this evaluation, the eMSCA has chosen to perform its own exposure assessment. This assessment is based on the information contained in registrations as they stood in January 2019. The eMSCA has chosen not to perform quantitative exposure assessments for the potentially obsolete professional and consumer use scenarios.

7.12.1.2 Exposure assessment performed by the eMSCA

7.12.1.2.1 Worker

To assess inhalation exposure to TPP where it is handled in non-aerosol forming processes, the eMSCA has adopted a similar approach to that used by the registrants and derived exposure estimates based on the saturated vapour concentration adjusted to take account of the rate of release to air from an open surface and the rate of removal due to natural ventilation.

To take account of the impact of risk management measures such as the use of local exhaust ventilation (LEV), the registrants have applied one of three "nominal efficiency tiers" with tier 3 equating to measures that will achieve a 99% reduction. The eMSCA notes that in order to achieve such reductions, specialised systems or combinations of measures (e.g. the use of respiratory protective equipment (RPE) to supplement LEV) are likely to be required. However, no information has been provided in CSRs to indicate how the registrants foresee this level of exposure mitigation will be achieved. For its own assessment therefore, the eMSCA used the default LEV efficiencies given in the ECETOC TRA tool v3 (or the Advanced REACH tool (ART) for aerosol forming processes).

Note to registrants: ECHA's Information Requirements and Chemical Safety Assessment (IR & CSA) guidance Chapter R14, section R14.5.2.2 Ventilation (ECHA, 2016), indicates that for an LEV system, 95% effectiveness or higher is only likely to be achieved where ventilation and engineering controls are specially designed and/or integrated into the equipment, expertly commissioned and tested regularly to ensure the system continues to operate at the intended high level of performance. It is not clear from the information currently provided in CSRs how such a high level of performance is expected to be achieved, nor is it made clear in the exposure scenario that the use of RPE in addition to LEV may be necessary. Further details/advice to downstream users should be provided in the exposure scenario to make clear what measures should be implemented, and what management systems and training should be introduced to ensure these measures continue to provide the required level of protection.

The registrants chose to use the exposure estimates generated by the ECETOC TRA tool to assess inhalation exposure during aerosol forming processes. The eMSCA disagrees with this approach. It is clearly stated in the technical documentation for the TRA tool that

aerosol forming processes are outside its applicability domain. Using the TRA tool in this way will introduce greater uncertainty into the exposure calculations. The eMSCA has instead used the ART to assess airborne exposure during aerosol forming processes (PROCs 7 and 10). In the absence of specific information about the products that are used and processes that are operated, the eMSCA made assumptions about the the scale of processs and the conditions under which processes are operated (the input parameters used by the eMSCA are listed in Appendix 2, tables A2 and A3).

Note to Registrants: The IR & CSA Guidance Chapter R14, section R.14.6.6 Use of Exposure Estimation Tools (ECHA, 2016), states that users of modelling tools should ensure the tool is used within the published boundaries. Where modelling tools are used for situations outside their applicability domains, the exposure estimates should only be used in the assessment as supporting evidence. Registrants should therefore update their CSRs with an appropriate assessment for aerosol forming processes or provide a scientific justification indicating why the exposures calculated with the ECETOC TRA tool are representative for the use situation to which they are being applied. Any risk management measures (or combinations of risk management measures) that are identified as necessary to achieve safe use must be clearly described in exposure scenarios.

The eMSCA used the ECETOC TRA tool (v3) to assess dermal exposure for all activities. A validation study published in 2017 reported that the performance of this tool appeared to be in the range of the performance of other dermal exposure models (Marquart et al, 2017). The tool was found to overestimate exposure for activities with a low potential for dermal exposure. Where dermal exposure is expected to be higher, e.g. activities which may generate significant surface contamination, the tool predicted lower exposures than the corresponding measured data. For the purposes of this assessment, the eMSCA has taken account of the use of gloves only where these are specified in exposure scenarios. Where registrants differ in relation to the use (or not) of gloves, or differ in the level of protection that needs to be provided by the gloves, the eMSCA has applied the higher level of risk management. This approach was taken on the basis that all registrants self-classify TPP as a potential skin sensitiser (Skin Sens 1 or Skin Sens 1B) meaning that users of this substance and mixtures containing this substance at a concentration of 1% or more should be taking measures to minimise worker skin exposure.

Manufacture

TPP is manufactured in a predominantly closed batch process with only occasional opportunities for exposure as a result of sampling activities. Manufacture is described with PROCs 1, 2, 3, 4, 8a, 8b, 9 and 15. Most stages of the process take place at elevated temperatures. LEV is in use at all stages of the process except PROC 1 (this PROC applies to closed processes and LEV is not a relevant RMM).

Table 27: Parameters used in the eMSCA's calculations for manufacture

Contributing scenario	Assessment parameters	RMMs applied in calculations
PROC 1	Activity performed for up to 8 hours, substance used as such (100%), RMMs as specified.	Gloves Assigned Protection Factor (APF) 5
PROC 2		LEV, no gloves
PROC 3		LEV, no gloves
PROC 4		LEV, gloves APF 5
PROC 8a		LEV, gloves APF 5
PROC 8b		LEV, gloves APF 10
PROC 9		LEV, gloves APF 10

PROC 15		LEV, no gloves

Formulation, packing, distribution

Formulation of TPP is described by PROCs 1, 2, 3, 4, 5, 8a, 8b, 9 and 15. As for manufacture, LEV is in use at all stages of the process except PROC 1.

Table 28: Parameters used in the eMSCA's calculations for for formulation, packing, distribution.

Contributing scenario	Assessment parameters	RMMs applied in calculations
PROC 1	Activity performed for up to 8 hours, substance used as such (100%), RMMs as specified.	Gloves APF 5
PROC 2		LEV, no gloves
PROC 3		LEV, no gloves
PROC 4		LEV, gloves APF 5
PROC 5		LEV, no gloves
PROC 8a		LEV, gloves APF 5
PROC 8b		LEV, gloves APF 10
PROC 9		LEV, gloves APF 10
PROC 15		LEV, no gloves

Use as an intermediate

Most intermediate uses for TPP take place under SCC and the eMSCA has chosen not to perform a quantitiative assessment for use under SCC. This assessment applies to intermediate use not under SCC which is described in registrations by PROCs 1, 2, 3, 4, 8a, 8b and 15. LEV is in use at all stages of the process with the exception of PROC 1.

Table 29: Parameters used in the eMSCA's calculations for use as an intermediate not under SCC.

Contributing scenario	Assessment parameters	RMMs applied in calculations
PROC 1	Activity performed for up to 8 hours, substance used as such (100%), RMMs as specified.	Gloves APF 5
PROC 2		LEV, no gloves
PROC 3		LEV, no gloves
PROC 4		LEV, gloves APF 5
PROC 8a		LEV, gloves APF 5
PROC 8b		LEV, gloves APF 10
PROC 15		LEV, no gloves

Use as a stabiliser in polymer (covers manufacture of polymer, use of polymer to manufacture articles and the service life of articles)

TPP may be used as an antioxidant in plastics and rubber. TPP is formulated into the polymer blend which is then used to create articles covered by article categories (AC) 10 and 13. Manufacture of polymers is described by PROCs 1, 2, 3, 4, 5, 6, 8a, 8b, 9 and 14. LEV is in use at all stages of the process with the exception of PROC 1.

Table 30: Parameters used in the eMSCA's calculations for manufacture of formulated polymer.

Contributing scenario	Assessment parameters	RMMs applied in calculations
PROC 1	Activity performed for up to 8 hours, substance used as such (100%), RMMs as specified.	Gloves APF 5
PROC 2		LEV, no gloves
PROC 3		LEV, no gloves
PROC 4		LEV, gloves APF 5
PROC 5		LEV, no gloves
PROC 8a		LEV, gloves APF 5
PROC 8b		LEV, gloves APF 10
PROC 9		LEV, gloves APF 10

Use of the formulated polymer to produce articles is described by PROCs 5, 6, 7, 8a, 8b, 9, 10, 12, 13, 14, 21 and 24. The concentration of TPP in formulated polymers is less than 5% and in many cases may be less than 1%. Registrants differ about the maximum potential concentration that may be present in formulated polymers.

To assess potential inhalation exposure, for non-aerosol forming processes, the eMSCA has not made any adjustment of exposure predictions based on the saturated vapour concentration to take account of the percentage of TPP in the polymer. This is likely to result in a very conservative assessment. For aerosol forming processes, the eMSCA has use the ART assuming a concentration band of 1-5%.

For the dermal calculations, the eMSCA has applied the maximum stated concentration across all registrations rather than using the concentration band approach adopted within the ECETOC TRA tool. This will result in a less conservative assessment.

The registrants have assessed exposure during the service life of polymers containing TPP using PROCs 14, 21 and 24. They state that they have taken a very precautionary approach and assumed that all of the TPP present in the formulated polymer is potentially available, but have not provided enough information to enable the eMSCA to understand how they have derived the quantitative exposure estimates given for PROCs 21 and 24 in their CSRs.

For its assessment, the eMCSA has used the ECETOC TRA tool version 3 to derive exposure estimates for both the inhalation and dermal routes assuming that exposure will be to a dust rather than a liquid aerosol for PROCs 21 and 24(a) (these PROCs are not applicable for handling liquids). Rather than using the concentration band modifier adopted within the ECETOC TRA tool, the concentration of TPP in dusts released during processing of articles is based on the maximum stated concentration across all registrations. It is assumed that all of the TPP in the dust is potentially available, no attempt has been made to take account of any impact on exposure of the migration of TPP through the polymer.

Table 31: Parameters used in the eMSCA's calculations for use of formulated polymers.

Contributing scenario	Assessment parameters	RMMs applied in calculations
PROC 5	Activity performed for up to 8 hours, substance in a mixture, RMMs as specified.	Gloves APF 5
PROC 6		Gloves APF 5
PROC 8a		Gloves APF 5
PROC 8b		No RMMs applied
PROC 9		No RMMs applied
PROC 12		No RMMs applied
PROC 13		Gloves APF 5
PROC 14		No RMMs applied
PROC 7*		LEV, no gloves
PROC 10*		LEV, no gloves
PROC 21		No RMMs applied
PROC 24(a)		No RMMs applied

* A complete list of the assessment parameters used for the ART assessment of inhalation exposure is given in Appendix 2, tables A2 (PROC 7) and A3 (PROC 10).

Use in coatings and adhesives (covers manufacture of coatings and adhesives, their use and the service life of articles)

The manufacture of coatings and adhesives is described by PROCs 1, 2, 3, 5 and 8b. LEV is in use at all stages of the process except PROC 1.

Table 32: Parameters used in the eMSCA's calculations for manufacture of coatings and adhesives.

Contributing scenario	Assessment parameters	RMMs applied in calculations
PROC 1	Activity performed for up to 8 hours, substance used as such (100%), RMMs as specified.	Gloves APF 5
PROC 2		LEV, no gloves
PROC 3		LEV, no gloves
PROC 5		LEV, no gloves
PROC 8b		LEV, gloves APF 10

Use of coatings and adhesives containing TPP and the service life of articles to which TPP containing coatings and adhesives have been applied is described by PROCs 7, 8a, 8b, 9, 10, 13, 14, 21 and 24. TPP containing coatings or adhesives may be applied to articles covered by ACs 10 and 13. The concentration of TPP in coatings and adhesives is less than 5%.

To assess potential inhalation exposure, for non-aerosol forming processes, as before, the eMSCA has not adjusted the saturated vapour pressure calculation to take account of the percentage of TPP in the coating/adhesive which is likely to result in a very conservative assessment. For aerosol forming processes, the eMSCA has use the ART assuming a concentration band of 1-5%.

For the dermal calculations, the eMSCA has applied the maximum stated concentration across all registrations rather than using the concentration band approach adopted within the ECETOC TRA tool. This will result in a less conservative assessment.

The registrants have assessed exposure during the service life of coated articles using PROCs 14, 21 and 24 but have not provided enough information to enable the eMSCA to understand how they have derived the quantitative exposure estimates given for PROCs 21 and 24 in their CSRs. For its assessment, the eMCSA has used the ECETOC TRA tool version 3 to derive exposure estimates for both the inhalation and dermal routes assuming that exposure will be to a dust rather than a liquid aerosol for PROCs 21 and 24(a) (these PROCs are not applicable for handling liquids). Rather than using the concentration band modifier adopted within the ECETOC TRA tool, the concentration of TPP in dusts released during processing of coated articles is based on the maximum stated concentration across all registrations. It is assumed that all of the TPP in the dust is potentially available.

Table 33: Parameters used in the eMSCA's calculations for use of coatings/adhesives.

Contributing scenario	Assessment parameters	RMMs applied in calculations
PROC 8a	Activity performed for up to 8 hours, substance in a mixture, RMMs as specified.	Gloves APF 5
PROC 8b		Gloves APF 5
PROC 9		Gloves APF 10
PROC 13		Gloves APF 5
PROC 14		No RMMs applied
PROC 7*		LEV, no gloves
PROC 10*		LEV, no gloves
PROC 21		No RMMs applied
PROC 24(a)		No RMMs applied

* A complete list of the assessment parameters used for the ART assessment of inhalation exposure is given in Appendix 2, tables A2 (PROC 7) and A3 (PROC 10).

Use to manufacture lubricants

The manufacture of lubricants is described by registrants in several ways, some registrants explicitly state that in this process, TPP is reacted to form another substance hence this use meets the definition of an intermediate use. Others do not make this claim. and also include potentially obsolete scenarios covering industrial and professional use of lubricants containing <1% TPP.

Table 34: Parameters used in the eMSCA's calculations for lubricant formulation

Contributing scenario	Assessment parameters	RMMs applied in calculations
PROC 2	Activity performed for up to 8 hours, substance used as such (100%), RMMs as specified.	LEV, no gloves
PROC 3		LEV, no gloves
PROC 4		LEV, gloves APF 5
PROC 5		LEV, no gloves
PROC 8a		LEV, gloves APF 5

PROC 8b		LEV, gloves APF 10
PROC 9		LEV, gloves APF 10
PROC 15		LEV, no gloves

Waste and recycling

CSRs do not contain separate scenarios for waste and recycling, but the service life scenarios cover activities that are relevant for the waste and recycling sector. The eMSCA has therefore not performed separate exposure assessments for waste and recycling.

Cleaning and maintenance

It is not clear to the eMSCA how periodic cleanining and maintenance has been addressed by registrants.

Note to registrants: REACH Annex 1 section 0.3 states that the chemical safety assessment shall consider all stages of the life cycle. The IR & CSA Guidance Chapter R14, section 14.5.1 indicates that this includes periodic cleaning and maintenance such as cleaning machinery and vessels between batches, changing filters or maintenance of reservoirs of processing fluids, etc. The guidance recommends that specific contributing scenairos should be provided for these activities but it is currently not possible for the eMSCA to identify these contributing scenarios in registrations. Registrants should ensure that contributing scenarios for perodic cleaning and maintenance are clearly identified in registrations and that sufficient descriptive information is provided to identify the specific activities (e.g. wiping vessels using hand tools, automated cleaning of pipes, manually changing filters, etc) that are covered.

7.12.1.2.2 Consumer

According to information obtained by the PSRC in 2015, TPP is not supplied to consumers as the substance itself or as a component in mixtures. The eMSCA has therefore assumed that consumer use does not occur and has not carried out a quantitative exposure assessment for consumer use.

Although consumers do not appear to be supplied with TPP or mixtures containing TPP, consumer exposure is possible during the service life of articles. This exposure will depend on the types of articles that are made with TPP containing polymers or coatings and the rate at which TPP migrates out of such articles. CSRs do not provide sufficient information on either of these aspects to enable a realistic quantitative exposure assessment to be performed and a literature search performed by the eMSCA did not identify relevant information. Qualitatively, since TPP needs to remain in polymers/coatings in order to perform as an effective antioxidant, the rate of migration is likely to be low. Also, since TPP readily hydrolyses to form phenol and phosphorus acid, any TPP that has migrated to the surface of a polymer is expected to readily hydrolyse as a result of contact with moisture in the air. For these reasons, the eMSCA expects that exposure to TPP during the service life of articles, excluding situations where such articles undergo mechanical manipulation such as sanding, sawing or drilling, will be very low.

7.14.2. Exposure related to the environment

The manufacture, tonnages and uses for TPP in to the environment are as described for human health exposure in Section 7.15.1. Registrants' Chemical Safety Reports (CSRs) containing their environmental exposure assessments, are available in the IUCLID

registration dossiers and they have each been consulted..Exposure estimates have been determined using the ECETOC TRA model. The eMSCA has not conducted an in-depth evaluation or re-run EUSES or ECETOC TRA exposure modelling but has considered the reliability and appropriateness of the key input parameters (e.g. phys/chem endpoints for TPP) and assumptions about patterns of use in the modelling, i.e. the environmental release categories (ERC) and process categories (PROC) used.

TPP itself is not envisioned to be persistent or present in environmental compartments at meaningful levels due to its rapid degradation. For the environment the modelling therefore principally focuses on predicted exposure estimates for the main hydrolytic degradant, phenol - and these are compared with the available PNEC values for phenol taken from the ECB 2006 Risk Assessment Report for phenol (see Section 7.8.4) . The eMSCA has checked that the calculations and input parameters were also appropriate and consistent with those previously determined for phenol.

The emission scenarios and input parameters are basically similar in each CSR, although some just focus on the uses relevant for that Registrant. The Lead Registrant has produced combined calculations based on a 2014 TPP Registrant survey, including tonnages for all of the registered uses, including intermediates and imports as well as manufacture. Not all individual CSRs have been updated with the most recent usage information.

Some of the fractional releases to water and emission factors are varied from the standard default values assumed by each ERC. These are based on other figures proposed by, e.g. OECD Emission Scenario Documents or by the Registrants themselves - but they have not been not corroborated by the eMSCA.

Predicted Environmental Concentrations of phenol in water range from, e.g. 0.122 µg/L for wide dispersive use outdoors of long-life articles - to 0.59 µg/L for manufacture of coatings and adhesives. For sewage treatments plants (STP) they range from 0.0008 - 0.0052 mg/L and for soil from 0.0002 - 0.003 mg/kg dry weight. PEC values have not been produced for sediment as the potential for (and risk from) exposure of sediment to phenol was discounted in the ECB RAR (2006).

Since, based on information in this Conclusion Report, neither TPP nor its degradants are considered environmentally hazardous, the environmental exposure assessment has not been considered in further detail.

It is noted however, that all Registrants should bring their exposure modelling up to date based on the latest available usage information.

7.14.3. Combined exposure assessment

Combined exposure has not been addressed by the registrants. Information obtained by the PSRC in 2015 found that TPP and mixtures containing TPP are not supplied for consumer use. Also, given that exposure of humans via the environment is expected to be negligible, there does not appear to be a need to perform a quantitative exposure assessment for combined exposure.

7.15. Risk characterisation

7.16.1. Human Health

The health concerns driving the risk characterisation for human health are neurotoxicity and skin sensitisation. TPP is also classified as a skin and eye irritant and, based on the results of an oral LD50 value, it meets the criteria for classification with Acute toxicity 4.

Taking into account the severity of effects at seen at the dose level identified by the registrants as a LOAEL and that mild effects were still apparent at the dose level identified

by the registrants as a NOAEL, the eMSCA calculated its own DNELs rather than rely on the registrants DNELs. For workers, the eMSCA has calculated long-term systemic DNELs of 0.029 mg/m^3/8hr (inhalation) and 0.0083 mg/kg/day (dermal). The equivalent values for consumers are 0.007 mg/m^3/24 hrs (inhalation) and 0.004 mg/kg/day (dermal and oral). In calculating the long-term dermal DNEL values, the eMSCA has taken a precautionary approach. These have been derived by route-to-route extrapolation from oral data assuming that absorption via the gut and via skin are quantitatively the same, i.e. 100%. Since TPP has an octanol water partition coefficient of around 6, this implies that dermal uptake will be much slower than uptake from the gut, also that the percentage dermal uptake is likely to be much lower (it is more likely that TPP will accumulate in the stratum corneum with only a small amount of TPP, if any, crossing out of this barrier into the lower layers of the epidermis and dermis). For this reason, the eMSCA has also calculated a dermal DNEL assuming that only 10% of the applied dose crosses the skin to understand how this would impact the RCRs for each scenario.

The eMSCA has not calculated DNELs for short-term effects. Based on the toxicological profile of this substance (it is classified as a skin and eye irritant), the most likely effect from transient peak exposure will be site of contact irritation in the respiratory tract. There are no data to enable a short-term inhalation DNEL to be calculated for this effect. The only situation where TPP might be inhaled in sufficient quantities to cause site of contact irritation is where mixtures containing TPP are sprayed giving the potential for aerosols to form. Since registrants recommend RMMs to limit potential airborne exposure for this situation, the eMSCA does not identify a concern.

Workers

Using the registrants DNELs and the exposure values calculated by the registrants using the ECETOC TRA tool V2, RCRs < 1 have been obtained for every exposure scenario.

Using the eMSCA's DNELs and the exposure values estimated by the eMSCA, all RCRs combined are greater than 1 even where the lower level of skin absorption is assumed. Table 35 presents the PROCs giving rise to the highest RCRs for each scenario. Interestingly, when the eMSCA used the ECETOC TRA tool V3 to calculate dermal exposure using the OCs and RMMs described by the registrants and compared these values with the dermal DNEL calculated by the registrants, RCRs > 1 were obtained for PROCs 5 and 8a where TPP is used as the substance itself. ECETOC technical report 114, Appendix B indicates that one of the improvements implemented in the TRA tool V3 is an increase in the dermal exposure estimates for PROCs 5 and 8a where LEV is in use. This change may explain why RCRs >1 have been calculated with version 3 but not version 2. This finding suggests registrants should routinely revisit their exposure assessments when modelling tools are updated to ensure that changes made during the update do not impact their substance risk assessments.

Table 35: Risk characterisation ratios calculated by the eMSCA using its own exposure values and DNELs for PROCs giving rise to the highest RCRs for each scenario.

Scenario	Activity giving rise to highest RCRs	RCR inhalation	RCR dermal assuming 100% (and 10%) dermal absorption	RCR combined assuming 100% (and 10%) dermal absorption
Manufacture	PROC 1	4.5	0.84 (0.08)	5.3 (4.58)
	PROC 8a	2.9	32.5 (3.25)	35.4 (6.15)
Formulation	PROC 1	4.5	0.84 (0.08)	5.3 (4.58)
	PROC 5/8a	2.9	32.5 (3.25)	35.4 (6.15)
Use as an	PROC 1	4.5	0.84 (0.08)	5.3 (4.58)

intermediate	PROC 8a	2.9	32.5 (3.25)	35.4 (6.15)
Manufacture of polymer	PROC 1	4.5	0.84 (0.08)	5.3 (4.58)
	PROC 5/8a	2.9	32.5 (3.25)	35.4 (6.15)
Use of formulated polymer	PROC 8b	2.9	25.3 (2.53)	28.2 (5.43)
	PROC 7	8.3	3.6 (0.36)	11.9 (8.66)
	PROC 10	0.8	49.4 (4.9)	50.2 (5.7)
Service life of formulated polymers	PROC 21	1.55	4.8 (0.48)	6.4 (2.03)
	PROC 24(a)	0.52	4.8 (0.48)	5.3 (1.00)
Manufacture of coatings/adhesives	PROC 1	4.5	0.84 (0.08)	5.3 (4.58)
	PROC 5	2.9	32.5 (3.25)	35.4 (6.15)
Use of coatings/ adhseives	PROC 8a/8b/13	2.9	9.6 (0.96)	12.5 (3.86)
	PROC 7	8.3	3.6 (0.36)	11.9 (8.66)
	PROC 10	0.8	49.4 (4.94)	50.2 (5.7)
Service life of coated articles	PROC 21	3.1	9.6 (0.96)	12.7 (4.06)
	PROC 24(a)	1.03	9.6 (0.96)	10.6 (1.99)
Lubricant formulation	PROC 1	4.5	0.84 (0.08)	5.3 (4.58)
	PROC 5/8a	2.9	32.5 (3.25)	35.4 (6.15)

Inhalation

Looking first at the inhalation route, it is important to reflect that for non-aerosol forming processes, the exposure estimates from which these RCRs are derived are based on conservative estimates of the maximum potential airborne exposure. TPP is a low volatility substance and, in the absence of measured data, worst case estimates have been made about the potential for this substance to become airborne when it is handled in non-aerosol forming processes. The eMSCA does not therefore consider that RCRs of up to 4.5 for non-aerosol forming processes indicate an unacceptable risk.

The calculations for PROCs 7 and 10 are based on assumptions made by the eMSCA which aimed to generate higher rather than lower exposure estimates. It is not clear how closely these assumptions match the true conditions of use, for example the eMSCA assumed an LEV efficiency of only 50% whereas the registrants indicate an efficiency of 99% is required. If this level of protection is achieved, the inhalation RCR for PROC 7 reduces to 0.17. The eMSCA has identified a need for registrants to provide further details/advice to make clear what measures should be implemented to achieve the required level of protection, and the management systems and training that should be introduced to ensure the controls remain effective. The high RCR calculated by the eMSCA for PROC 7 (industrial spraying) highlights the importance of this additional information.

Dermal

The eMSCA has identified that TPP meets the criteria for classification with Skin Sens. 1A. A quantitative risk characterisation has not been performed for this hazard but the eMSCA has obtained very high RCRs in its quantitative risk characterisation for systemic effects when 100% dermal absorption is assumed. Many RCRs are still above 1 if the lower value of 10% is assumed and it should also be reflected that the exposure estimates used to calculate these RCRs are not precautionary. The eMSCA applied concentration directly in

calculations rather than using the default concentration band and assumed the higher level of risk management was applied where there were differences between registrants.

It is possible that the ongoing dermal absorption study will provide evidence that allows dermal DNELs to be recalculated and this may reduce these dermal RCRs. Even with this additional data, it is not certain that dermal RCRs will fall below 1. This raises a concern for workers if adequate and sufficient measures are not implemented to minimise skin exposure throughout the supply and downstream use chain. Registrants should work with their downstream users to identify ways of working that limit direct exposure of workers to TPP. Extended SDSs for TPP and mixtures containing TPP must be clear about the types of gloves and other chemical protective clothing that are needed for tasks where there is the potential for direct skin contact with TPP, giving the information that REACH requires registrants to provide about suitable glove materials, thicknesses and breakthrough times. Ideally this should be accompanied by statements about the need for downstream users to implement PPE management programmes including worker training (if they do not have such programmes already) as indicated in the decision issued on 2 December 2015.

Service life

In relation to the RCRs > 1 obtained for processing of articles, these assessments were based on precautionary assumptions about the concentration of TPP in the article, the potential for TPP to migrate out of polymers/coatings and the absence of any controls to limit worker exposure. Registrants should consider providing more information in their CSRs to enable the eMSCA to refine its exposure assessment or change the risk management approach they are recommending.

Since the service life assessments also cover activities that are relevant to waste and recycling and, particularly if the registrants decide that specific OCs and RMMs are required, the registrants should consider developing specific scenarios for these life cycle stages and communication tools to ensure this information reaches waste and recycling companies.

Consumer exposure via articles

A quantitative assessment has not been performed for incidental exposure during the everyday use of articles that arises due to the migration of TPP out of polymers or coatings. Given the low potential for exposure that is expected in this situation, the eMSCA anticipates that there will be a low risk for systemic effects and also skin sensitisation.

Conclusion of the risk characterisation for human health

TPP meets the criteria for classification with Skin Sens 1A and it is a recommendation from this evaluation that a proposal for harmonised classification should be submitted to ECHA's Risk Assessment Committee.

In addition, several recommendations are made to registrants to improve aspects of the human health hazard and exposure assessments presented in their CSRs.

The following aspects of registrations need further work:

- Registrants should take note of the comments made in relation to the human health hazard assessment and provide the requested additional information.

- Registrants that have not updated their dossiers since the PSRC survey was carried out need to consider if the findings are relevant to their downstream use chain and update their dossiers as necessary. If any registrant identifies relevant professional or consumer uses they must provide in their registration the additional information requested for these uses in the decision issued on 2 December 2015.

- All registrants should note that the assessment of airborne exposure to liquid aerosols is outside the applicability domain for the ECETOC TRA tool. Registrants should therefore update their CSRs with an appropriate assessment for aerosol forming processes or provide a scientific justification indicating why the exposures calculated with the ECETOC TRA tool are representative for the use situation to which they are being applied. If the justification is based on the assumption that the ECETOC TRA prediction will be precautionary, this must be supported by measurements demonstrating the maximum airborne concentrations that can be obtained for representative uses of TPP and TPP containing mixtures.

- All registrants must ensure that exposure scenarios provide clear descriptions of the risk management measures (or combinations of risk management measures) required to achieve the levels of exposure mitigation that are necessary to use TPP safely. In relation to airborne exposure, if situations are identified where RPE is needed to supplement other engineering controls, information must be given in exposure scenarios on the type of RPE that should be used, the required protection factor and the appropriate filter. It will be useful to supplement this information with advice on the implementation of a RPE management programme including worker training.

- The decision issued on 2 December 2015 asks registrants to provide more information about suitable gloves. The IR & CSA Guidance Chapter R14, section R.14.5.3 states that "It is an absolute requirement that the barrier properties of the glove material are known to be adequate to ensure the substance does not migrate through the material of the glove during the proposed use. It is important that gloves are sufficiently described in the IUCLID dossier and the CSR so that there is assurance that suppliers of substances and formulations, can effectively communicate (in section 8 of the Safety Data Sheet) the correct information to downstream users. Important information on gloves relates to those materials that are effective and over what duration they are effective. It is also useful to provide information on common glove materials that are known not to be effective as a barrier". It will be useful to supplement this information with advice on the implementation of a glove management programme, good housekeeping practices and worker training. Registrants should also provide advice on additional chemical protective clothing to prevent skin contact with other areas of the body than hands if there is the potential for such skin contact.

- Registrants should consider developing specific scenarios to cover periodic cleaning and maintenance activities such as cleaning machinery and vessels between batches or changing filters etc.

- Currently insufficient information has been provided in CSRs to enable the eMSCA to understand the exposure assessment approach that has been taken by the registrants to assess service life. Registrants should ensure that the basis for their exposure assessment approach is clearly described in the CSR. In light of the high RCRs obtained by the eMSCA for both the inhalation and dermal routes, and since processing of articles in the ways covered by these service life assessments are relevant for the waste and recycling sectors, registrants should consider developing specific scenarios for these sectors. Communications to waste and recycling companies on risk management measures should ideally include information about the polymer and article types where TPP may be present.

All registrants should take account of the actions to improve their CSRs suggested in this report when registrations are next updated.

7.16.2. Risk characterisation related to the environment

As described in other Sections, the risk assessment to the environment from TPP is based on that from phenol due to the rapid degradation of TPP to phenol and phosphorous acid. Inorganic phosporous acid is described as essentially non-hazardous to the environment, so risk characterisation for the environment combines the PNEC values derived for phenol from Section 7.8.4 with the Predicted Exposure Concentrations (PEC) values for phenol derived from exposure modelling, see Section 7.15.2.

Registrant's CSRs have been consulted and they each provide Risk Characterisation Ratios (RCR) for the environment based on the various uses outlined in Section 7.15. All of the RCRs (for all relevant emission/release sources) are much less than 1.

These RCRs indicate that environmental exposures to phenol from the release of TPP are all well below any of the risk levels. No specific risk management measures (RRMs) related to environmental exposure/risk have been identified.

Since, based on information in this Conclusion Report, neither TPP nor its degradants are considered environmentally hazardous, the environmental risk assessment has not been considered in further detail. It is noted however, that all Registrants should bring their exposure modelling and risk assessments up to date based on the latest available usage information.

Risk characterisation for PBT/vPvB substances

Neither TPP nor its primary hydrolysis products, phenol or phosphorous acid, are considered to be PBT or vPvB. Therefore, no further risk characterisation or assessment is required.

Indirect exposure of humans via the environment

Given that TPP readily hydrolyses in the environment, indirect exposure of humans via the environment is expected to be negligible and does not raise concerns.

7.16.3. Overall risk characterisation

Human health (combined for all exposure routes)

For workers, RCRs >1 have been calculated by the eMSCA for both the inhalation and dermal routes. The high inhalation RCRs are likely to be the result of precautionary assumptions about the potential for TPP to become airborne and assumptions made by the eMSCA about the efficiency of RMMs where insufficient information was provided in registrations. The high dermal RCRs may in part be due to precautionary assumptions about dermal absorption potential, but could also signal the need for registrants to increase the stringency of the RMMs they are recommending to manage risks to the skin. Including Skin Sens 1A in the harmonised classification will support efforts made by registrants to improve measures to minimise skin exposure and this action is a recommendation from this evaluation.

A qualitative risk characterisation has been performed for consumers and this has not identified any concerns. Based on information obtained by the PSRC survey indicating that TPP and mixtures containing TPP are not supplied for consumer use, no concerns are identified for possible combined workplace and consumer exposure.

Environment (combined for all exposure routes)

Overall, Risk Characterisation Ratios determined for representative uses of TPP (based on exposure and effects data for phenol only) indicate that environmental risks from all industrial, professional and consumer uses of TPP will be low. On this basis, no further information or risk management measures are required.

7.16. References

A number of unpublished studies were included in the registration dossier, and have been used during this evaluation. These are not referenced here.

Human health references

Abou-Donia MB. (1992) Triphenyl Phosphite: A Type II Organophosphorus Compound-Induced Delayed Neurotoxic Agent. In J. Chambers and P. Levi (Eds), Organophosphates: Chemistry, Fate and Effects (pp 327 – 351). San Diego, CA: Academic Press.

Basketter, D. A., Andersen, K. E., Liden, C., van Loveren, H., Boman, A., Kimber, I., Alanko, K., and Berggren, E. 2005. Evaluation of the skin sensitizing potency of chemicals by using the existing methods and considerations of relevance for elicitation. *Cont. Derm.* **52**:39-43.

ECB (2006) European Union Risk Assessment Report - Phenol. European Chemicals Bureau. https://echa.europa.eu/documents/10162/1ca68f98-878f-4ef6-914a-9f21e9ad2234

ECETOC (2004) ECETOC TRA Targeted Risk Assessment. Technical Report No. 93. European Centre for Ecotoxicology and Toxicology of Chemicals 4 Avenue E. Van Nieuwenhuyse (Bte 6), B-1160 Brussels, Belgium.

EC Health & Consumer Protection DG (2004) Guidance document on dermal absorption. Sanco/222/2000 rev.7. https://ec.europa.eu/food/sites/food/files/plant/docs/pesticides_ppp_app-proc_guide_tox_dermal-absorp-2004.pdf

ECHA (2010). Guidance on information requirements and chemical safety assessment. Chapter R8: characterisation of dose [concentration]-response for human health. 2013.http://echa.europa.eu/documents/10162/13632/information_requirements_r8_en.pdf.

ECHA (2017) Guidance on Information Requirements and Chemical Safety Assessment. Chapter R.7c: Endpoint Specific Guidance v3.0. https://echa.europa.eu/documents/10162/13632/information_requirements_r7c_en.pdf/e2e23a98-adb2-4573-b450-cc0dfa7988e5

ECHA (2012). Guidance on information requirements and chemical safety assessment. Part E: risk characteristion.2013. http://echa.europa.eu/documents/10162/13632/information_requirements_part_e_en.pdf.

ECHA (2016). Guidance on information requirements and chemical safety assessment. Chapter R14: Occupational Exposure Assessment version 3.0. https://echa.europa.eu/documents/10162/13632/information_requirements_r14_en.pdf.

Fehrenbacher, M.C. and Hummel, A.A. (1996). Evaluation of the mass balance model used by the Environmental Protection Agency for estimating inhalation exposure to new chemical substances, *American Industrial Hygiene Association Journal* **57:** 526-536.

IPCS (International Programme on Chemical Safety). 2002. Endocrinology and endocrine toxicology. In *Global Assessment of the State-of-the-Science of Endocrine Disruptors.* eds. T. Damstra, S. Barlow, A. Bergman, R. Kavlock, and G. Van Der Kraak, pp 11-32. (Geneva: World Health Organization, WHO/IPCS/EDC 02.2).

Marquart H., et al. (2017). Validation of the dermal exposure model in ECETOC TRA, Annals of Work Exposures and Health 61(7): 854-871.

OECD (2004). Emission Scenario Document on Plastics Additives. Paris, OECD Environmental Health and Safety Publications. Series on Emission Scenario Documents No. 3, ENV/JM/MONO(2004)8.

OECD (2018). Guidance document on standardised test guidelines for evaluating chemicals for endocrine disruption. 150, 1-524. Paris, Environment Directorate, Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology. Series on Testing and Assessment.

PEST (Plastics Exposure Scenario Team) (2010). Generic Exposure Scenarios (GES) for chemicals used in the plastics industry. http://pestpublic.plastics.net/public/ .

Suuronen, K., Pesonen, M., Henriks-Eckerman, M.-J., Aalto-Korte, K. (2012). Triphenyl phosphite, a new allergen in polyvinylchloride gloves. Contact Dermatitis, 68, 42-49.

Vandevenne, A., Ghys, K., Dahlin, J., Ponten, A., Kerre, S. (2013). Allergic contact dermatities caused by triphenyl phosphite in poly(vinyl chloride) gloves. Contact Dermatitis, 68, 181-192.

Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., Mortelmans, K., and Speck, W. 1987. Salmonella mutagenicity tests: III. Results from the testing of 255 chemicals. Environmental Mutagenesis, 9(9):1-110. *Environmental Mutagenesis* **9**, no. 9:1-109.

Environmental references

Al-Lohedan, H. A. 1991. Micellar effects upon acid catalyzed hydrolysis of triphenyl phosphite. *Phosphorous, Sulfur, Silicon Relat. Elem.* **63**, no. 3-4:261-271.

European Chemicals Bureau. (2006). European Union risk assessment report: phenol. Volume 64, 1-240.

OECD (2000). Guidance document on aquatic toxicity testing of difficult substances and mixtures. OECD Environmental Health and Safety Publications, Paris. Series on Testing and Assessment No. 23, ENV/JM/MONO(2000)6.

US EPA. (2010). Bioaccumulation modeling results from BCFBAF v.3.00. Report date: 2010-03-12.

US EPA. (2001). Ecological Structure Activity Relationship Model (ECOSAR).The latest version of ECOSAR is available from the EPA, OPPT New Chemicals Program web site at: http://www.epa.gov/oppt/newchems/tools/21ecosar.htm.

7.17. Abbreviations

AC	Article Category
AF	Assessment factor
ART	Advanced REACH tool
BCF	Bioconcentration factors
CSR	Chemical Safety Report
DNEL	Derived no-effect level
ECB	European Chemicals Bureau
ECETOC TRA	European Centre for Ecotoxicology and Toxicology of Chemicals Targeted Risk Assessment
ED	Endocrine disruptor
eMSCA	Evaluating Member State Competent Authority
EPA	Environmental Protection Agency
ES	Exposure Scenario
EU	European Union
EUSES	European Union System for the Evaluation of Substances
EUTGD	European Union Technical Guidance Document
FOB	Functional observation battery
IR&CSA	Information Requirements and Chemical Safety Assessment
IUCLID	International Uniform Chemical Information Database
LEV	Local exhaust ventilation
LLNA	Local lymph node assay
Mg	Milligram
mg/kg bw	milligram per kilogram of bodyweight
mg m^{-3}	milligrams per cubic metre
mmol/l	millimoles per litre
mmol/kg bw	millimoles per kilogram of bodyweight
min	minute
MS	Member State of the EU
N/A	not applicable
OC	Operating conditions
PC	Product category
PND	Post-natal day
PPE	Personal protective equipment
PROC code	Process Code
PSRC	Phosphite Stabilisers REACH Consortium
RCR	Risk Characterisation Ratio
RMM	Risk management measure
RPE	Respiratory protective equipment
SCC	Strictly Controlled Conditions
SU	Sector of Use
t	Tonne
tpa	tonnes per annum
TPP	Triphenyl phosphite
UK	United Kingdom
µg/kg bw	microgram per kilogram bodyweight
WWTP	waste water treatment plants

7.18. Appendices

Appendix 1 – Literature search parameters

Parameters used for the literature search conducted by the eMSCA in January 2019 to identify supplementary information relevant for the human exposure assessment. No relevant additional information was found.

Table A1

Set 1 – Chemical Substance	**Set 2 – Exposure**
Triphenyl phosphite or Triphenyl Phosphite or TPP or TPPi triphenylphosphite or "Phostacon TPP" or "202-908-4" or "101-02-0" or "ADK STAB TPP" or "Doverphos 10" or "G-special UTTO 10W-30r" or "Lankromark LE65" or "Mark CH 66" or "Markphos TPP" or "Rostabil TPP" or "Weston TPP" or Phosphorous acid, triphenyl ester or PHOSPHOROUS ACID, TRIPHENYL ESTER or Triphenylphosphite	expose* or exposure* or exposing or work* or consumer* or domestic or monitor* or surveillance or occupation* or paraoccupation* or dust or article or "migration rate" or antioxidant or stabiliser or stabilizer
Fields: ti,su	Fields: ti,su
Limiters: Exclude animal studies No language limit Chemical 1 – no date limit	
Databases: Medline Embase Toxfile Web of Science	

Appendix 2 – Input parameters for ART calculations

The eMSCA has used the ART to estimate exposures for aerosol generating activities associated with the use of formulated polymers containing TPP and the use of coatings/adhesives containing TPP (PROCs 7 and 10). In doing this, it has been necessary for the eMSCA to make several assumptions about the nature of the work activities and of the workplaces where these activities take place. The following text identifies where assumptions have been made and the reasons why particular input parameters have been chosen. The eMSCA recommends that if the registrants are considering using the ART to refine their own exposure estimates, they obtain additional information from their downstream users from which to identify representative input parameters.

The following assumptions have been made by the eMSCA:

The parameters covering activity duration and substance emission potentials are derived from information contained in registrations.

The parameters covering activity emission potentials are intended to reflect working practices that will lead to higher rather than lower exposure estimates but which seem relevant based on the scenario titles.

It has been assumed that effective housekeeping practices are in place because this would be expected in workplaces that are complying with workplace health and safety legislation.

Since registrations indicate that LEV is in use, a generic option has been selected because the exposure scenarios do not provide information about the specific type of LEV that should be used.

No information is provided in registrations about general room ventilation. Since the calculations for non-aerosol forming processes assume a ventilation rate of around 1 air change per hour, this value has been applied in the ART calculations.

It is assumed that each activity takes place in a busy workroom where the activity is being performed by more than one worker at a time, hence there is the potential for exposure from both near- and far-field sources.

The input parameters and predicted exposure levels are listed in tables A2 and A3.

Spraying of polymers or coatings/adhesives containing TPP

Table A2: Input parameters used by the eMSCA to assess worker exposure to TPP during spraying activities covered by PROC 7.

Activity duration	480 minutes
Near field exposure	
Operational conditions	
Substance emission potentials	
Substance product type	Liquids
Process temperature	Room temperature (15-25°C)
Vapour pressure	0.069 Pa
Liquid weight fraction	Small (1-5%)
Viscosity	Medium
Activity emission potential	
Activity class	Surface spraying of liquids
Situation	Moderate application rate (0.3-3 l/minute)
Spray direction	Only horizontal or downward
Spray technique	Spraying with no or low compressed air use
Surface contamination	
Process fully enclosed?	No
Effective housekeeping practices in place?	Yes
Dispersion	
Work area	Indoors
Room size	Any size workroom
Risk management measures	
Localised controls	
Primary	Other LEV systems (50% reduction)
Secondary	No localised controls (0% reduction)
Dispersion	
Ventilation rate	1 air change per hour
Far field exposure	
Operational conditions	
Substance emission potentials	
Substance product type	Liquids
Process temperature	Room temperature (15-25°C)
Vapour pressure	0.31 Pa
Liquid weight fraction	Small (1-5%)
Viscosity	Medium
Activity emission potential	
Activity class	Surface spraying of liquids
Situation	Moderate application rate (0.3-3 l/minute)
Spray direction	Only horizontal or downward
Spray technique	Spraying with no or low compressed air use
Risk management measures	
Localised controls	
Primary	Other LEV systems (50% reduction)
Secondary	No localised controls (0% reduction)
Segregation	No segregation (0% reduction)
Predicted exposure levels	
Mecanistic model results	
75th percentile full-shift exposure	0.24 mg/m^3
Interquartile confidence interval	0.11 – 0.51 mg/m^3

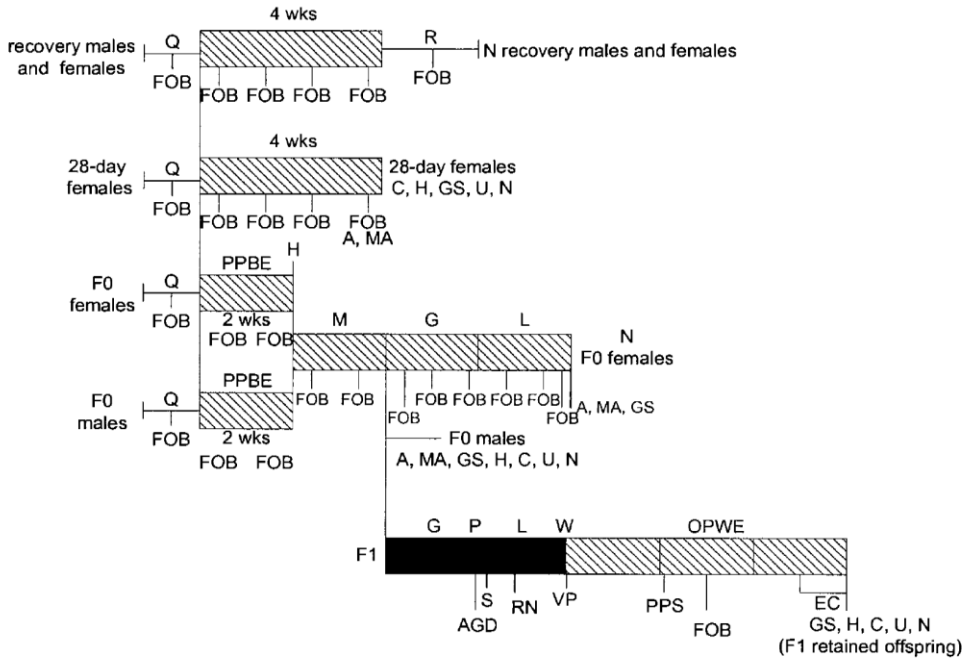
Roller or brush application of polymers or coatings/adhesives containing TPP

Table A3: Imput parameters used by the eMSCA to assess worker exposure to TPP during roller or brush application (PROC 10).

Activity duration	480 minutes
Near field exposure	
Operational conditions	
Substance emission potentials	
Substance product type	Liquids
Process temperature	Room temperature (15-25°C)
Vapour pressure	0.069 Pa
Liquid weight fraction	Small (1-5%)
Viscosity	Medium
Activity emission potential	
Activity class	Spreading of liquid products
Situation	Spreading of liquids at surfaces or work pieces > 3m^2/hour
Surface contamination	
Process fully enclosed?	No
Effective housekeeping practices in place?	Yes
Dispersion	
Work area	Indoors
Room size	Any size workroom
Risk management measures	
Localised controls	
Primary	Other LEV systems (50% reduction)
Secondary	No localised controls (0% reduction)
Dispersion	
Ventilation rate	1 air change per hour
Far field exposure	
Operational conditions	
Substance emission potentials	
Substance product type	Liquids
Process temperature	Room temperature (15-25°C)
Vapour pressure	0.069 Pa
Liquid weight fraction	Small (1-5%)
Viscosity	Medium
Activity emission potential	
Activity class	Spreading of liquid products
Situation	Spreading of liquids at surfaces or work pieces > 3 m^2/hour
Risk management measures	
Localised controls	
Primary	Other LEV systems (50% reduction)
Secondary	No localised controls (0% reduction)
Segregation	No segregation (0% reduction)
Predicted exposure levels	
Mechanistic model results	
75th percentile full-shift exposure	0.024 mg/m^3
Interquartile confidence interval	0.011 – 0.051 mg/m^3

Appendix 3 – Study design of the combined repeated dose and reproduction/developmental screening study (unpublished, 2004)

Figure 1. Study Design



Key:

H = Hematology
R = Recovery period
N = Necropsy
FOB = Functional observational battery
C = Clinical chemistry
A = Auditory function
MA = Motor activity
GS = Grip strength
Q = Quarantine (~7 days)
PPBE = Parental prebreed exposure (2 wks)
M = Mating (2 wks)
G = Gestation (3 wks)
L = Lactation (3 wks)
U = Urinalysis
P = Parturition
W = Weaning
VP = Acquisition of vaginal patency (females)
PPS = Acquisition of preputial separation (males)
OPWE = Offspring postwean exposure (7 wks)
EC = Estrous cyclicity (F1 females, last 3 wks of OPWE)
AGD = Anogenital distance on pnd 0
S = Standardize litters to 10 pups on pnd 4
RN = Observation of retained nipples and areolae (F1 males, pnd 11-13)

Direct exposure
Possible indirect exposure during gestation (transplacental) and lactation (translactational)
No exposures for recovery males and females