SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

Tris(methylphenyl) phosphate

EC No 809-930-9

CAS No 1330-78-5

(Previously registered as EC number 215-548-8, CAS RN 1330-78-5)

Evaluating Member State(s): The Netherlands

Dated: 12 November 2021[1]

[1] Version updated on 18 April 2023 to clarify the content, as highlighted on page 3 of this document.

Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2014

Before concluding the substance evaluation a Decision to request further information was issued on: 26 July 2016

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.

Version	Changes	Month & year of updated version
1.0	Section 7.1. Table 3 - content clarified Section 7.9.8. - content clarified	April 2023

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[2].

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.

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

Contents

Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

The Substance, Tris(methylphenyl) phosphate, EC number 809-930-9 (hereafter referred to as TCP) was originally selected for substance evaluation to clarify concerns about:

- (suspected) PBT
- wide dispersive use
- aggregated tonnage
- potential neurotoxic effects of the substance in aviation uses

During the evaluation also another concern was identified. The additional concern was:

- High risk characterisation ratios (RCRs)

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Two compliance checks were performed for the TCP registration dossier that were concluded in 2014. The compliance checks were related to the provided analytical information and the compositions of the registered substance.

3. CONCLUSION OF SUBSTANCE EVALUATION

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

Table 1

CONCLUSION OF SUBSTANCE EVALUATION Conclusions	
Need for follow-up regulatory action at EU level	x
Harmonised Classification and Labelling	
Identification as SVHC (authorisation)	
Restrictions	
Other EU-wide measures	
No need for regulatory follow-up action at EU level	

4. FOLLOW-UP AT EU LEVEL

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

In 2016, the substance evaluation led to the Decision of information requests on toxicity, absorption, DNEL derivation and exposure. A 90-day neurotoxicity inhalation study was requested to obtain information on neurotoxicity as the substance is a suspected neurotoxin due to the established neurotoxicity of the very closely related ortho-TCP isomer and reported neurological symptoms in cabin crew.

Moreover, a dermal absorption study was requested as the provided information on dermal absorption was unreliable. In parallel, exposure information for numerous exposure scenarios was requested.

As a result, the Registrants have updated their dossier and revised the exposure assessment, taking an updated DNEL into account. The new information and revised exposure assessment clarified previous issues on hazard, exposure, and risk management.

The DNELs derived by the eMSCA are lower than the DNELs in the dossier. The exposure concentrations are underestimated, because the Registrants used higher protection factors (e.g. 99% protection instead of 95%) and lower percentiles of the exposure distribution (80th percentile instead of 90th percentile). As a result, the eMSCA derives RCR values > 1 for several uses indicating the potential for an unacceptable risk for human health.
A follow-up is necessary to explore the most appropriate risk management measure to mitigate the identified risks.

Based on the information provided during the Substance Evaluation and the subsequent updated Registration Dossier the eMSCA concludes that there is a human health risk for several current uses of TCP. The eMSCA will further discuss these uses and health risks together with the most appropriate regulatory action in a separate Risk Management Options Analysis (RMOA) document.

4.1.1. Harmonised Classification and Labelling

Not applicable.

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

Not applicable.

4.1.3. Restriction

Not applicable.

4.1.4. Other EU-wide regulatory risk management measures

Not applicable.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

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

Not applicable

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

Indication of a tentative plan is not a formal commitment by the evaluating Member State. A commitment to prepare a REACH Annex XV dossier (SVHC, restrictions) and/or CLP Annex VI dossier should be made via the Registry of Intentions.

Table 2

FOLLOW-UP		
Follow-up action	**Date for intention**	**Actor**
RMOA	2022	the Netherlands

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

The Substance, TCP (EC number 809-930-9) was originally selected for substance evaluation to clarify concerns about:

- (suspected) PBT
- wide dispersive use
- aggregated tonnage
- potential neurotoxic effects of the substance in aviation uses

During the evaluation also another concern was identified. The additional concern was:

- High risk characterisation ratios (RCRs)

Table 3 briefly describes the outcome of the substance evaluation based on the information provided in 2019 and 2020 following the Decision on TCP in 2016.

Table 3

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
Potential neurotoxic effects of the substance in aviation uses	Concern refuted[3] Sufficient information available for the eMSCA to evaluate the neurotoxicity for specified uses. Concern not substantiated, no further action.
PBT	Concern refuted Not substantiated, no further actions.
Dermal absorption	Concern confirmed Sufficient information available for the eMSCA to evaluate the dermal absorption. The eMSCA recalculated the dermal DNEL and RCRs. Concern for high RCRs substantiated further action required.
Exposure assessment	Concern confirmed Sufficient information available for the eMSCA to evaluate the exposure scenarios. Concern for high RCRs substantiated further action required.
DNEL derivation	Concern confirmed Sufficient information available for the eMSCA to evaluate the DNEL derivation. Concern for high RCRs substantiated further action required.
High risk characterisation ratios (RCRs)	Concern confirmed Sufficient information available for the eMSCA to evaluate the RCRs. Concern for high RCRs substantiated further action required.

[3] This conclusion outcome does not concern uses that include exposure to either ultrafine particles, including nanoparticles, that may contain TCP, or heated oils containing TCPs.

7.2. Procedure

The decision-making procedure is described in the Decision on TCP dated 26 July 2016 (European Chemicals Agency 2016). Briefly, information requests in the Decision were to provide a 90-day inhalation neurotoxicity study, an *in vitro* dermal absorption study, an exposure scenario for pilots and cabin crew during flights and information on the DNEL derivation, worker exposure assessments with details on the RMMs and medical and clinical investigations.

During the process the eMSCA and Registrants had informal communication to exchange information related to methodological issues of the 90-day neurotoxicity study by inhalation.

In July 2018 the Registrants informed the eMSCA of a delay in the dossier update due to the complexity of the requested 90-day neurotoxicity study by inhalation.

Since April 2019 the updated registration dossier has been evaluated by the eMSCA. During the evaluation, the eMSCA requested further detailed information on the performed histopathology analysis in the 90-day neurotoxicity study by inhalation. The Registrants subsequently provided the requested information on the 14th January 2021. The eMSCA concluded that the Registrant fulfilled the information requests as outlined in the Decision with respect to the concerns specified under Section 7.1.

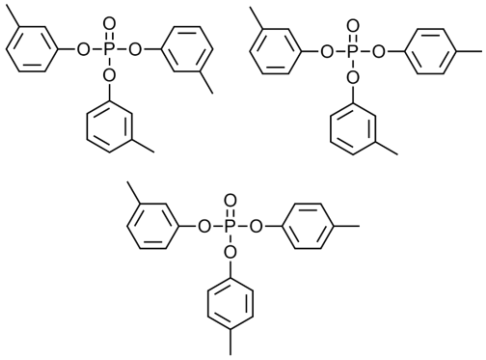
7.3. Identity of the substance

Table 4

SUBSTANCE IDENTITY	
Public name:	Tris(methylphenyl) phosphate (Reaction mass of 3-Methylphenyl di-4-methylphenyl Phosphate and 4-Methylphenyl di-3-methylphenyl Phosphate and tris(3-methylphenyl)phosphate)
EC number:	809-930-9
CAS number:	1330-78-5
Index number in Annex VI of the CLP Regulation:	-
Molecular formula:	C21H21O4P
Molecular weight range:	368.37
Synonyms:	Disflamoll TKP Disflamoll TKP-P Durad 125 From CO Reofos 908 From CO TCP/TXP Kronitex TCP Kronitex TCP-S PHOSPHORIC ACID TRICRESYL ESTER PHOSPHORIC ACID, TRIS(METHYLPHENYL) ESTER PHOSPHORIC ACID, TRITOLYL ESTER PX 3843 TCP TRICRESYL PHOSPHATE TRITOLYL PHOSPHATE

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

Structural formula:



Multiconstituent.

Table 5

Constituent			
Constituents	**Typical concentration**	**Concentration range**	**Remarks**
Tri-m-tolyl phosphate EC: 209-241-8		Between 89 and 100%	
4-Methylphenyl di-3-methylphenyl Phosphate		Between 89 and 100%	
3-Methylphenyl di-4-methylphenyl Phosphate		Between 89 and 100%	
Tri-o-tolyl phosphate EC: 201-103-5			Impurity

7.4. Physico-chemical properties

Table 6

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	Liquid
Vapour pressure	4.7×10^{-6} Pa at 20 °C 2.3×10^{-4} Pa at 50 °C
Water solubility	0.271 mg/L
Partition coefficient n-octanol/water (Log Kow)	5.93
Flammability	Flashpoint >200 °C
Granulometry	Not relevant
Explosive properties	Non explosive
Oxidising properties	No
Stability in organic solvents and identity of relevant degradation products	Not relevant
Dissociation constant	Not relevant

7.5. Manufacture and uses

7.5.1. Quantities

Table 7

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

7.5.2. Overview of uses

Table 8

USES	Use(s)
Uses as intermediate	
Formulation	This substance is used in the following products: polymers, adhesives and sealants, coating products, laboratory chemicals and photo-chemicals. This substance is used in the following activities or processes at workplace: transfer of chemicals, transfer of substance into small containers, closed batch processing in synthesis or formulation, batch processing in synthesis or formulation with opportunity for exposure, mixing in open batch processes, production of mixtures or articles by tabletting, compression, extrusion or pelletisation, laboratory work, closed, continuous processes with occasional controlled exposure and roller or brushing applications.
Uses at industrial sites	This substance is used in the following products: polymers, lubricants and greases, metal working fluids, heat transfer fluids, laboratory chemicals and hydraulic fluids. This substance is used in the following areas: scientific research and development and formulation of mixtures and/or re-packaging. This substance is used for the manufacture of machinery and vehicles, plastic products, chemicals and rubber products. This substance is used in the following activities or processes at workplace: transfer of chemicals, transfer of substance into small containers, batch processing in synthesis or formulation with opportunity for exposure, closed batch processing in synthesis or formulation, closed processes with no likelihood of exposure, closed, continuous processes with occasional controlled exposure and mixing in open batch processes.
Uses by professional workers	This substance is used in the following products: polymers, hydraulic fluids, metal working fluids, lubricants and greases, adhesives and sealants and coating products. This substance is used in the following areas: printing and recorded media reproduction, formulation of mixtures and/or re-packaging and scientific research and development. This substance is used for the manufacture of machinery and vehicles, plastic products, and mineral products (e.g., plasters, cement). This substance is used in the following activities or processes at workplace: transfer of chemicals, closed processes with no likelihood of exposure, roller or brushing applications, non-industrial spraying, production of mixtures or articles by tabletting, compression, extrusion or pelletisation, the low energy manipulation of substances bound in materials or articles, heat / pressure transfer fluids in closed systems,

	treatment of articles by dipping and pouring and transfer of substance into small containers.
Consumer Uses	*This substance is used in the following products: polymers, adhesives and sealants, coating products, hydraulic fluids and photo-chemicals.*
Article service life	*ECHA has no public registered data on the use of this substance in activities or processes at the workplace.*

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

There is no harmonized classification for this substance.

7.6.2. Self-classification

- In the registration(s):
  H361: Suspected of damaging fertility or the unborn child. Testicular effects; oral route.
  H400: Very toxic to aquatic life.
  H410: Very toxic to aquatic life with long lasting effects.

• The following hazard classes are in addition notified among the aggregated self-classifications in the C&L Inventory*:* No notification available.
This is probably due to a substance identity change in 2015. The EC number used for this substance prior to 2015 is 215-548-8.

7.7. Environmental fate properties

The eMSCA did not evaluate the environmental fate properties.

7.8. Environmental hazard assessment

The eMSCA did not evaluate the environmental hazard assessment

7.9. Human Health hazard assessment

7.9.1. Toxicokinetics

The dermal absorption of TCP was evaluated as part of the evaluation of the high RCRs and the DNELs derived. The low assumed dermal absorption percentage together with relatively high dermal exposures in the registration dossier were of concern. The substance evaluation led to the conclusion that the information provided in the registration dossier was inadequate to predict the absorption of TCP nor to justify the lower than default dermal absorption percentage used in the CSR. Hence, an in vitro dermal absorption test was requested.

The Registrant subsequently performed this study and updated the registration dossier accordingly. The eMSCA evaluated the provided information of the conducted absorption study and notes the following:

- No deviations from guidelines were detected.
- The test compound was representative for the registered compound.
- *In vitro* studies with human skin should preferably use split-thickness (200–400 µm) (dermatomed) skin and be from the abdomen, back, breast or upper leg. As a minimum

requirement, results from at least four replicates should be analysed in *in vitro* studies in line with the recommendations given in EC test guideline B.44 (in vivo dermal absorption). The evaluated study used dermatomed human skin samples (340-406 µm) from 4 female donors and the formulation was applied in duplicate resulting in a total of 8 replicates per test substance concentration.

- The test substance was applied without occlusion (open coverage) which does not reflect the human exposure conditions that include chemically resistant gloves with (other) appropriate dermal protection. However, due to the low vapour pressure (4.7 x 10^{-6} Pa), significant evaporation, and subsequent underestimation of the dermal absorption, is not anticipated by the eMSCA.
- The results do not appear to be dose dependant (40% is the anomaly). This was also noted by the Registrant. No explanation was found for this anomaly.
- The study tested three dosing concentrations: 100%, 40% and 5%. These concentrations are similar to the formulation and use of the registered substance, where 100% and 5% are the most used.
- The study used ethanol to increase the solubility of the test substance in the receptor fluid to avoid insolubility as limiting factor in the determination of the absorption potential of the skin.

The eMSCA considers the conducted absorption study to provide sufficient information for the assessment of the dermal absorption of the registered Substance.

The Registrant used the information from the conducted absorption study for the derivation of the dermal absorption (%) to be used in the risk assessment. In the summary and discussion by the Registrant of the toxicokinetics, the eMSCA notes the following:

- The Registrant used the dose directly absorbed (6,81%) from the formulation with the lowest amount of TCP (5% v/v) in the risk assessment
- According to the study results, at 24 hours, following an 8-hour exposure to the TCP 5% v/v formulation, a mean of less than 75% of absorption into the receptor fluid occurred within the first half of the experiment and 89.49% of the applied dose was considered removeable from the application site.

The eMSCA agrees with the Registrant that the formulation with the lowest amount of TCP (5% v/v) is the most suitable for the determination of the dermal absorption to be applied in the risk assessment. However, as less than 75% of absorption into the receptor fluid occurred within the first half of the experiment, the dose potentially absorbed (10.43%) (including the stratum corneum (tape strips 3-20)) should be taken for the risk assessment. The Registrant argues that the artificial enhancement of the receptor fluid with 40% ethanol increased the permeation results through lipid extraction during the prolonged 24-hour test conditions. Therefore, the Registrant concluded the dermal absorption data may over-predict the absorption, however, for the purpose of risk assessment, the highest value seen to be adsorbed was utilised for risk assessment (6.81%).

The eMSCA notes that the OECD Guidance Notes on Dermal Absorption clearly requires enhancement of receptor fluids (up to 50% ethanol) to increase the solubility for lipophilic substances. This is needed to avoid the significant underestimation of absorption in *in vitro* absorption studies of lipophilic substances compared to the *in vivo* data. The Registrant's reference to table 1 of the OECD Guidance Notes on Dermal Absorption is flawed as this table describes the influence of the formulation (the vehicle), not the receptor fluid, on permeability of the skin after application. In this study, the vehicle was mineral oil that, according to the same table, can reduce the skin permeation of lipophilic permeants. The same applies to the study by Van der Merwe 2005 that the Registrant refers to, as this study looked at the influence of ethanol in the formulation instead of the receptor fluid. Therefore, the eMSCA does not agree with the argumentation brought forward by the

Registrant that the required artificial enhancement of the receptor fluid with ethanol over predicts the absorption.

Therefore, for the purpose of risk assessment, the eMSCA uses 10.43% as dermal absorption percentage.

7.9.2. Acute toxicity and Corrosion/Irritation

Not evaluated by the eMSCA; outside the scope of the identified concerns

7.9.3. Sensitisation

Not evaluated by the eMSCA; outside the scope of the identified concerns

7.9.4. Repeated dose toxicity

Not evaluated by the eMSCA; outside the scope of the identified concerns

7.9.5. Mutagenicity

Not evaluated by the eMSCA; outside the scope of the identified concerns

7.9.6. Carcinogenicity

Not evaluated by the eMSCA; outside the scope of the identified concerns

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

Not evaluated by the eMSCA; outside the scope of the identified concerns

7.9.8. Specific investigations – Neurotoxicity

The neurotoxicity of TCP was investigated due to concerns related to the potential neurotoxic effects of (isomers of) TCP, used as additive in engine oils in airplane engines and subsequent exposure of TCP, or breakdown products, to cabin crew, pilots, and passengers. Due to a lack of data covering all aspects of possible neurotoxicity and due to a lack of inhalation studies, it could not be determined whether the DNEL in the CSR covers these potential neurotoxic effects. Therefore, a 90-day repeated dose neurotoxicity study by inhalation (nose only) with additional neurological endpoints was requested using a representative composition of the registered Substance with the following adaptations and additions:

- In addition to the general test method the assessment of learning and memory (using the Morris Water Maze test or avoidance tests).
- The histopathology shall be designed in such way to detect neuro-inflammation and neural degradation by identification of:
    - (starting) degeneration of neurons (e.g., by silver staining or fluoro-jade staining).
- Inflammation processes focusing on microgliosis (e.g., Iba-1 antibodies or NSA reactive microglia staining) and astrogliosis (e.g., GFAP staining).
- In addition to the general test method the determination of cholinesterase activity in the brain of at least 3 animals per dose group at the end of exposure.
- In addition to the general test method the inclusion of recovery group in the high dose group for a recovery period of at least 1 month with the determination of all observational and histopathological parameters.

- An adaptation to the motor activity test by dividing the test arena into a central and peripheral zone and include additional analyses to determine changes in activity patterns as indication for anxiety and hyperactivity.

The Registrant subsequently performed this study and updated the registration dossier accordingly. The eMSCA evaluated the provided information of the conducted neurotoxicity study and notes the following:

- The study was carried out according to guidelines OPPTS 870.6200 (Health Effects Test Guidelines OPPTS 870.6200 Neurotoxicity Screening Battery) and the OECD Test Guideline 424 (Neurotoxicity Study in Rodents) with minor modifications.
- The study exposed Crl:CD(SD) rats by nose-only to 6 hours/day of the test substance (dose groups) or filtered air (control group) for 90 consecutive days. Dose groups consisted of approximately 100, 300 or 1000 mg/m^3 of the test substance. Additional animals were assigned to the control and highest dose group to include a recovery group.
- The assessment of learning and memory was performed using a water filled 8-unit T-maze.
- Histopathology staining was performed on the following sections:
    - Brain sections, sections of cervical, thoracic and lumbar spinal cord were stained with hematoxylin and eosin (H&E), Luxol fast blue/cresyl violet (LFB/CV), Bielchowsky's silver and Fluorojade B. In addition, brain spinal cord sections were immunohistochemically stained for glial fibrillary acidic protein (GFAP) and Iba-1.
    - Trigeminal ganglia/nerves and dorsal root ganglia (with associated dorsal and ventral nerve roots) were stained with H&E, LFB/CV and Bielschowsky's silver.
    - Longitudinal sections of peripheral nerves (sciatic at mid-thigh and sciatic notch, tibial, sural, and peroneal nerves) were stained with H&E. Cross-sections of the peripheral nerves were stained with toluidine blue.
    - The eyes, optic nerves, and gastrocnemius muscle were stained with H&E.
- Brain cholinesterase activity was measured in the brains after homogenising using an assay based on a modification of the Ellman reaction.
- The motor activity test consisted of an opaque, open top enclosure (1 m x 1 m with 0.38 m walls). The area of the enclosure was divided into 2 zones, the central zone (0.7 m x 0.7 m) and the peripheral zone (0.15 m from the periphery on all sides). A video tracking software and system was used to measure the time spent and the number of entries into each zone.
- The test substance is well characterised and representative of the registered Substance.

The overall assessment by the eMSCA is that the study was performed according to the study design requested in the ECHA Decision. In general, the results (individual and group data) are reported adequately except that reporting of the histopathology section is rather limited and could be more informative, e.g., with regard to the results of the special stains used. At the request of the eMSCA, additional analyses on the histopathology and staining information were provided by the Registrants on 14 January 2021. More specifically, the eMSCA requested a more objective quantification of cell numbers in a predefined 'region of interest' (ROI) in the brain. Hereto, an unbiased estimate of selectively stained glial cells is obtained, i.e., total number of Iba1+ microglia and GFAP+ astrocytes within the ROI, a defined portion of the neocortex at the level of the thalamus. Furthermore, information is obtained about possible effects on the myelination process by estimating the g-score – ratio [axon diameter: total fiber diameter] – measured in two peripheral nerves, namely in the sural nerve (a predominantly sensory nerve) and in the tibial nerve (a mixed, mainly motor nerve). In addition, clear photographs of the different cell structures, selectively stained with special histochemical stains were added to the report.

The eMSCA considers the conducted neurotoxicity study to provide sufficient information for the assessment of the neurotoxicity of the registered Substance for the specified uses.

In the summary and discussion by the Registrant of the study results, the eMSCA notes the following:

- The Registrant considers an exposure level of 300 mg/m^3 to be the no-observed-adverse-effect level (NOAEL) for male systemic toxicity based on lower mean body weights and body weight gains for 1000 mg/m^3 group males, with corresponding effects on mean food consumption and food efficiency.
- The Registrant considers an exposure level of 1000 mg/m^3 to be the no-observed-adverse-effect level (NOAEL) for female systemic toxicity based on the lack of adverse effects at any exposure level.
- The Registrant considers an exposure level of 1000 mg/m^3 to be the no-observed-adverse-effect level (NOAEL) for both male and female neurotoxicity based on the lack of adverse neurotoxic effects.
- The Registrant notes the lower mean brain cholinesterase activities in the 1000 mg/m^3 group females at weeks 13 and 17 (recovery) compared to the control group females. The registrant considers these changes to be test substance related but non-adverse based on the small magnitude of the differences from the control group (≤12.0%), absence of corresponding behavioural effects in the females, and lack of a similar effect on brain cholinesterase activity in males at this exposure level.

The Registrant used the information from the conducted neurotoxicity study to determine the NOAEL for neurotoxicity and subsequently derive a DNEL for the evaluation of exposure of pilots and cabin crew to registered Substance. The Registrant does not use the information from the conducted neurotoxicity study to derive the long-term systemic effect DNELs for the worker or general public as more critical dose descriptors are available.

The eMSCA finds the statistically significant findings observed in some of the behavioural testing to be 'fortuitous findings' rather than to be determined as 'not test substance related'. After all, the test substance can affect the nervous system as demonstrated by the brain cholinesterase results. Neither the presence of 'random' statistically significant findings, nor the absence of a (linear) dose response relationship, provides hard evidence of any (causal) relationship to the test substance (a dose response curve need not necessarily be linear).

The eMSCA does not agree with the Registrants interpretation of the brain cholinesterase data and the conclusion regarding the NOAEL for neurotoxicity. The eMSCA is of the opinion that, after considering all available data provided in this study together with background knowledge on gender specific susceptibility of acetylcholinesterase inhibitions of organophosphates, the effects on acetylcholinesterase inhibition in the female rats at the high dose should be considered adverse and substance specific. Subsequently, the eMSCA considers the mid dose of 300 mg/m^3 as NOAEL for both systemic and neurotoxic effects in male and female rats.

7.9.9. Hazard assessment of physico-chemical properties

Not evaluated by the eMSCA, outside the scope of the identified concerns

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

The DNEL derivation of TCP was investigated to assess the risks associated with the use of TCP. The eMSCA noticed deviations from the default assessment factor for remaining interspecies differences. Therefore, further information was requested to justify the deviation of this assessment factor.

The Registrant subsequently used the default assessment factor for remaining interspecies differences and updated the registration dossier accordingly.

Table 9 presents the DNELs as derived by the Registrants and the DNELs used by the eMSCA in the evaluation of RCRs. The eMSCA did not evaluate the robustness of the chosen critical dose descriptor (Point of Departure (PoD)) for the DNEL derivations. As discussed in 7.9.1 and 7.9.8, the eMSCA uses 10.43% as dermal absorption percentage in the derivation of the dermal DNEL and considers the 300 mg/m^3 dose in the sub chronic inhalation study as NOAEL for neurotoxicity.

Table 9 Overview of DNELs

CRITICAL DNELS						
Endpoint of concern	**Type of effect**	**Critical study(ies)**	**Corrected dose descriptor(s) (e.g. NOAEL, NOAEC)**	**Registrants' DNEL**	**eMSCA remarks**	**eMSCA DNEL used in evaluation**
Repeated dose toxicity – dermal	Ceroid pigmentation of the adrenal cortex	2-year NTP study (CAS No. 1330-78-5) (1994) in B6C3F1 mice; oral	7 mg/kg/day (LOAEL), corrected for 5 day/week exposure and applying route-to-route extrapolation assuming 50% oral and 6.81% dermal absorption leads to 71.95 mg/kg/day	0.41 mg/kg/day (Worker)	The eMSCA does not agree with the dermal absorption percentage. An dermal absorption of 10.43% should be used instead when evaluating the RCRs	0.27 mg/kg/day (Worker)
Repeated dose toxicity – inhalation	Ceroid pigmentation of the adrenal cortex	2-year NTP study (CAS No. 1330-78-5) (1994) in B6C3F1 mice; oral	7 mg/kg/day (LOAEL), corrected for 5 day/week exposure; differences in metabolism (allometric scaling); light activity and applying route-to-route extrapolation assuming 50% oral and 100% inhalatory absorption leads to 4.56 mg/m^3	0.18 mg/m^3 (Worker)	-	0.18 mg/m^3 (Worker)

The eMSCA evaluated the 90-day inhalation neurotoxicity study in rats (2019) to derive a DNEL. According to the eMSCA the observed toxicity in this study do not lead to a lower DNEL for the inhalation route. The most critical repeated dose toxicity observed in this study was lower mean body weights and body weight gains with corresponding effects on mean food consumption and food efficiency at the highest dose tested. This results in a NOAEL of 300 mg/m^3. The same applies for the neurotoxic effects, which were observed at the highest dose tested and lead to a NOAEL of 300 mg/m^3 for neurotoxicity.

After correction for 5 day/week; 8 hours a day exposures and light activity the corrected dose descriptor is 211.3 mg/m^3. After applying assessment factors for the duration of the

study (2), intraspecies variation (5) and remaining toxicodynamics (2,5), the DNEL based on adverse effects in the requested 90-day inhalation neurotoxicity study would be 8.4 mg/m^3. This DNEL is clearly higher than the DNEL of 0.18 mg/m^3 derived based on adverse effects (ceroid pigmentation of the adrenal cortex) in the 2-years carcinogenicity study in mice. Therefore, the eMSCA agrees with the Registrants that the observed toxicity in the 90-day inhalation study does not lead to a lower DNEL.

For risk characterization, the toxicological effect that results in the most critical DNEL should be used. Therefore, for exposure of workers via the inhalation route, the DNEL of 0.18 mg/m^3 should be applied protecting against adrenal effects as well as neurotoxicity.

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

The eMSCA finds the information sufficient to assess the neurotoxic potential for the hazard assessment and related classification and labelling. The provided data does not meet the criteria for classification related to neurotoxic effects. Based on the provided data, the 90-day inhalation study on neurotoxicity does not lead to a more conservative DNEL.

The worker DNELs for long term exposure; systemic effects (including neurotoxicity) according to the eMSCA are:

Dermal: *0.27 mg/kg/day*

Inhalation: *0.18 mg/m^3*

7.10. Assessment of endocrine disrupting (ED) properties

7.10.1. Endocrine disruption – Environment

Not evaluated by the eMSCA, outside the scope of the identified concerns.

7.10.2. Endocrine disruption - Human health

Not evaluated by the eMSCA, outside the scope of the identified concerns.

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

Not evaluated by the eMSCA, outside the scope of the identified concerns.

7.11. PBT and VPVB assessment

There was an initial PBT concern based on a ready biodegradability test (OECD301D) that showed 24.2% oxygen consumption after 28 days, leading to the conclusion on non-ready biodegradability. In the subsequent PBT assessment, further P testing was waived based on observed hydrolysis. However, refitting the data presented in this study by the eMSCA lead to different conclusions, as a plateau in the hydrolysis seemed to give a much better fit to the data. Therefore waiving further P-testing based on this data was not considered acceptable.

Persistence

Nevertheless, there is much more degradation data available on tri-cresyl phosphate, presented in detail in a report on the Environmental risk evaluation of tricresyl phosphate (CAS 1330-78-5) by the UK Environment Agency (Brooke, Crookes et al. 2009), all leading to the conclusion that the substance can be considered not P or vP. An overview of the most relevant studies is given in Table 10 and can be found in the updated registration dossier.

Table 10. Most relevant degradation studies.

MOST RELEVANT DEGRADATION STUDIES			
OECD guideline	**test type**	**degradation**	**Remarks**
OECD301C	MITI-I, ready biodegradability	80% / 28 days	TCP synthesized from 70% m- and 30% p-cresol. Study evaluated by eMSCA
OECD301D	Closed Bottle, ready biodegradability	24.2% / 28 days	No measures were taken to improve bioavailability of the substance in the test
OECD302C	MITI-II, Inherent biodegradability	100% / 28 days (O_2) 100% / 28 days (GC) 97.8% / 28 days (UV-vis)	para-TCP
OECD302C	MITI-II, Inherent biodegradability	65.7% / 28 days (O_2) 82.6% / 28 days (GC) 81.6% / 28 days (UV-vis)	ortho-TCP
	River die-away (SCAS, acclimated sludge)	78.6% / 7 days (CO_2) 82.1% / 28 days (CO_2) 97-99% / 28 days (O_2)	commercially available TCP, isomeric composition not specified

The OECD TG 301C study does not specify the exact isomeric composition of the TCP mixture tested, but it states that the TCP was synthesized from 70% meta-cresol and 30% para-cresol, with only traces of ortho-cresol present in the starting agents. The anticipated reaction product mixture from these starting materials would be sufficiently close to the registered substance to be able to interpret this study and conclude that the substance (all its isomers) would be readily biodegradable.

The OECD TG 301D study was performed without any measures to increase the bioavailability of the (poorly water soluble) substance. The OECD Test Guideline states that insoluble and volatile substances may be assessed using this method if precautions are taken. Degradation values for insoluble substances may be falsely low unless the bottles are agitated periodically during the incubation. No agitation was undertaken during the study. As a result, it is considered that the lack of agitation has affected the outcome of the studies. This study is therefore deemed "not reliable" when considering the propensity of this material to biodegrade.

The first OECD TG 302C study in Table 10, showing 100% oxygen consumption after 28 days was performed with para-TCP, whereas the second OECD TG 302C study, giving 65.7% oxygen consumption after 28 days, was performed with ortho-TCP, an isomer of commercially available TCP at the time. Note that the ortho-isomer is not present in current day commercial TCP. It shows that the different isomers also have different propensities to biodegrade. The meta-isomer however is thought to be as biodegradable (or better) as the ortho-isomer, which is supported by the Bayer 1987 study where 70% meta-cresol was present in the reaction agents used to synthesize TCP, and the degradation test still reached 80% of the theoretical oxygen demand after 28 days.

Finally, the River die-away study is the closest to environmental degradation, although acclimated sludge is used, and it cannot be excluded that non-acclimated sludge would give lower degradation rates. Nevertheless, the combination of the OECD TG 301C ready biodegradability study (using non-acclimated sludge) combined with the results from these multiple inherent and simulation studies lead to the conclusion that the registered substance, despite uncertainties about the exact isomer compositions tested, can be regarded as readily biodegradable, and not P (or vP).

In the UK Environmental assessment report on TCP (Brooke, Crookes et al. 2009) even more degradation study results are presented, all leading to the conclusion that TCP is not P.

Bioconcentration

Log Kow values in de dossier of 5.93 (experimental), 6.3 (QSAR estimated, EPA KowWIN v1.68) both indicate the potential of this substance to bioaccumulate. However, several studies on bioconcentration of TCP in fish are available. Literature values for the bioconcentration factor (BCF) are generally well below 2000, with one exception: Muir (1984). In this study the measurement of total radioactivity for the para-TCP isomer yielded a value of 2768. The same study calculates BCF values based on parent substance of 310-770. Measurement of total radioactivity leads to overestimation of the Substance BCF.

One literature study using bleak (salt water species, exposure via water) is considered the most relevant, and this shows BCF values in the range of 400-800 (Bengtsson, Tarkpea et al. 1986). The same study also evaluates BCF via food (in fathead minnows) leading to BMF values of 0.06-0.6.

Again, the UK Environmental risk assessment for TCP (Brooke, Crookes et al. 2009) presents these studies, and concludes that the more reliable data based on parent compound analysis gives BCFs ranging from 310 to 800 l/kg. A conservative value of 800 is recommended for risk assessment. This is well below the B-criterion of 2000.

Therefore, the substance is not considered B (or vB).

Toxicity

As both the P- and the B-criterion are not fulfilled, the toxicity studies regarding T-criterion have not been evaluated in detail. As the Substance is considered a Reproductive toxicity Cat.2 by the Registrants, the T-criterion can be fulfilled. The lowest chronic NOEC for fish (0.32 ug/L), as reported in the UK risk assessment report, is well below the T-criterion of 0.01 mg/L (based on growth of embryo-larval stages of three spined stickleback (*Gasterosteus aculeatus*)). The Substance should therefore be considered T.

PBT overall conclusion

As the substance can be considered readily biodegradable, the substance is not P, and therefore not PBT. Evaluation of the available bioconcentration studies leads to the conclusion that the substance also does not reach the B-criterion for PBT assessment, as a worst-case representative value for BCF is 800 L/kg.

The substance is therefore not considered PBT or vPvB.

This data has been presented to the EU PBT Expert working group, November 2014, and after discussion the experts working group supported the conclusion that the substance is not PBT, as it is not fulfilling the P-criterion, and most likely also not fulfilling the B-criterion. Following this PBT assessment and conclusion, the Registrants have updated the registration dossier for TCP accordingly.

7.12. Exposure assessment

Shortcomings were identified in the initial registration dossier on TCP concerning the exposure assessment. Insufficient detail was available in the human exposure assessment to conclude on the adequacy of the RMMs currently in place.
Based on the information in the registration dossiers the estimation of the exposure cannot be verified. Furthermore, many estimates for dermal and inhalation exposure could not be reproduced by the eMSCA.

Therefore, the Registrants are requested to fill out omissions in the exposure assessments by including or adding:

1. An exposure assessment for the exposure scenario of pilots and cabin crew to the registered substance during flights, including the calculation of RCRs.

2. An enquiry of neurotoxic complaints among TCP exposed workers.
3. Detailed information on worker exposure for all scenarios, specifically:
    - The initial exposure estimates without modifiers
    - All values of the input parameters used in the models
    - All values of any additional modifiers used in the models and the details of personal protective equipment within each scenario, including the specifications for all personal protective equipment and engineering controls
    - A copy of the model inputs, modifiers and outputs.
    - A justification for all deviations from the default values
    - A quantification of the risk, taking into account all RMMs, leading to a final RCR.
4. A higher tier exposure assessment using realistic input variables, or perform exposure measurements, for exposure scenarios with process category PROC 7 (industrial spraying), PROC 11 (non-industrial spraying), PROC 10 (roller application or brushing) and PROC 19 (hand-mixing with intimate contact and only Personal Protective Equipment (PPE) available).
5. Reassessment of the professional worker exposure estimation for the use of photochemicals containing TCP using a model that is specifically made for worker exposure estimation (ES 11).
6. Combined inhalation exposure estimations for different sources of exposures when a time reduction factor is used.

Following the update of the registration dossier in 2019 new exposure information was provided which will be discussed below.

7.12.1. Human health (workers)

Exposure assessment for the exposure scenario of pilots and cabin crew to the registered substance during flights, including the calculation of RCRs.

The Registrant did not add the exposure scenario of pilots and cabin crew to the CSR, but delivered a separate document to the eMSCA in which RCRs were calculated. The eMSCA agrees with the Registrant that under normal operating conditions, seals are in place to functionally separate the engine oil containing TCP from the bleed air for use in the air-conditioning systems. The eMSCA does not agree with the Registrant that contamination of the bleed air with TCP and other engine oil additives occurs only in the event of a seal failure, which is an accidental event. The detection of TCP, although in low concentrations, in the cabin air during various monitoring studies may indicate the leakage of low levels of engine oil during normal operation conditions.

The eMSCA agrees with the Registrant to use publicly available exposure monitoring data of TCP for the calculation of RCRs. Three internationally published exposure monitoring studies were used to calculate the risk characterization ratios. Although the monitoring studies are not a complete overview of all available data, the eMSCA agree to use these studies as they represent >100 individual flight data measurements. In addition, a theoretical model is included for an unlikely worst-case scenario of the total discharge of an engine's lubricant into the engine bleed system. The eMSCA finds the information sufficient to assess the risks for pilots and cabin crew during flights.

The Registrant calculated inhalation RCRs, dermal RCRs and combined RCRs and concluded that all combined RCRs were extremely low. The highest inhalation RCR reported by the Registrant was based on the theoretical worst-case scenario. The eMSCA does not agree with both the inhalation DNEL and the dermal DNEL used by the Registrant in the document. As mentioned before, the eMSCA considers a different dermal absorption percentage to be more realistic and therefore a dermal DNEL of 0.27 mg/kg bw/day should be used. The Registrant derived a DNEL based on the 90-day neurotoxicity study, however, more sensitive dose descriptors for long term exposure; systemic effects are available. Although this exposure scenario focusses on neurological effects, the eMSCA uses the lowest DNEL available to assess the risk of systemic effects.

Based on the theoretical worst-case scenario and the eMSCA DNELs, RCRs are >1. However, the eMSCA agrees with the Registrant that this scenario is unlikely. The eMSCA is of the opinion that a reported maximal total TCP concentration of 37.7 µg/m^3 is representative. Based on the eMSCAs DNEL this leads to an inhalation RCR of 0.21. The eMSCA agrees to the dermal exposure of 0.1 ng/cm^2 and subsequent RCR << 1. The aggregated exposure and eMSCAs DNELs lead to a RCR of 0.21.

Enquiry of neurotoxic complaints among TCP exposed workers.

See confidential Annex

Detailed information on worker exposure for all scenarios

To allow an assessment of the adequacy of the risk management measures in place for the registered substance, the Registrant updated the registration dossier and provided risk assessments for the identified uses for systemic toxicity of the substance after repeated administration (inhalation and dermal).

Exposure modelling was applied to estimate both inhalation and dermal exposure. Inhalation exposure was estimated by ECETOC-TRA v3.0 or the Advanced REACH Tool (ART); dermal exposure was estimated by ECETOC-TRA v3.0 or RiskofDerm. ART and RiskofDerm were used when ECETOC-TRA v3.0 estimates were not within the application domain of the model.

The eMSCA assessed the occupational conditions (OCs) and risk management measures (RMMs) implemented to control long term exposure and considers them insufficient to control repeated exposure for several exposure scenarios. The eMSCA based this conclusion on the following information:

- Time-reduction factors were applied in contributing scenarios (CS) defined by a PROC, leading to RCR ≤ 1. Since workers may perform several CS within an ES, the RCRs of the CS should be summarized to guarantee safe use for that ES. The eMSCA is of the opinion that RCR > 1 may occur for several ES within manufacturing; formulation; use at industrial site and use by professional worker.
- Respiratory protection (rpe) and gloves are prescribed during the whole shift (i.e. 8 hours) to control exposure for many CS. Wearing personal protection should be minimized since wearing personal protection is extra stressful. Technical and organizational measures should be taken first to control exposure.
- Dermal exposure was initially estimated with ECETOC-TRA v3.0. The second-tier model RiskofDerm was applied in case dermal exposure estimations did not lead to safe use. According to the eMSCA:
    - the 90th percentile of the distribution in RiskofDerm should be used to estimate dermal exposure. The Registrant applied the 80th percentile in several ES within manufacturing; formulation; use at industrial site and use by professional worker.
    - a maximum dermal protection factor for the use of chemically resistant gloves is 95% in case of industrial use (also in case of full sealed hand and arm protection) and 90% in case of professional use. The Registrant applied higher protection factors, i.e., 99% for industrial use and 95% or 99% for professional use. This was the case in several ES within manufacturing; formulation; use at industrial site and use by professional worker.
- No RCR is calculated where TCP contaminated dust is generated. According to the eMSCA, exposure to TCP may occur through exposure to TCP contaminated dust.

Higher tier exposure assessment using realistic input variables (or exposure measurements) for PROCs that may lead to aerosol formation.

In the updated registration dossier, the Advanced REACH Tool (ART) was used to estimate inhalation exposure, and RiskofDerm was used to estimate dermal exposure for those PROCs that may lead to aerosol formation. All input parameters are available and the models output is presented. The eMSCA is of the opinion that this shortcoming in the initial

CSR had been resolved in the updated revised CSR.

Reassessment of the professional worker exposure estimation for the use of photochemicals containing TCP

The use of photochemicals containing TCP is not included as an ES in the updated registration dossier and subsequently this application is no longer supported.

7.12.2. Environment

Not evaluated by the eMSCA, outside the scope of the identified concerns

7.12.3. Combined exposure assessment

Not evaluated by the eMSCA, outside the scope of the identified concerns

7.13. Risk characterisation

As indicated in section 7.12.1, the eMSCA evaluation of several exposure scenarios lead to a RCRs>1 indicating human health risks are currently not controlled.

7.14. References

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7.15. Abbreviations

BCF: Bioconcentration Factor

CLP: Classification, Labelling and Packaging

CoRAP: Community Rolling Action Plan

CSR: Chemical Safety Report

eMSCA: evaluation Member State Competent Authority

ES: Exposure Scenario

LOAEL: Lowest-Observed-Adverse-Effect Level

NOAEL: No-Observed-Adverse-Effect Level

PBT: Persistent Bioaccumulating and Toxic

PROC: Process Category

RCR: Risk Characterisation Ratio

RMM: Risk Management Measure

RMOA: Risk Management Options Analysis

SVHC: Substance of Very High Concern

TCP: Tris(methylphenyl) phosphate