EUROPEAN CHEMICALS AGENCY

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DECISION ON SUBSTANCE EVALUATION PURSUANT TO ARTICLE 46(1) OF REGULATION (EC) NO 1907/2006

For Tris(methylphenyl) phosphate, CAS No 1330-78-5 (EC No 809-930-9) (previously registered with**EC No 215-548-8)**

Addressees: Registrant(s)[1] of Tris(methylphenyl) phosphate

This decision is addressed to the Registrant(s) of the above substance with active registrations pursuant to Article 6 of the REACH Regulation on the date on which the draft for the decision was first sent for comments. If Registrant(s) ceased manufacture upon receipt of the draft decision pursuant to Article 50(3) of the REACH Regulation, they did not become addressee(s) of the decision. A list of all the relevant registration numbers of the Registrant(s) that are addressees of the present decision is provided as an Annex to this decision.

Based on an evaluation by Bureau REACH on behalf of the Ministry of Infrastructure and the Environment as the Competent Authority of The Netherlands (evaluating MSCA), the European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 52 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

This decision is based on the registration dossier(s) on 4 May 2015, i.e. the day on which the draft decision was notified to the Registrant(s) pursuant to Article 50(1) of the REACH Regulation.

For the substance specified above, ECHA has issued different decisions depending on the type of information requested and the Registrant(s) in question. One decision is addressed individually to all Registrant(s) which are jointly responsible to provide the information required (this present decision). It contains requests to provide information on the toxicity of the substance, derived no effect levels (DNEL) and on worker exposure. ECHA has issued separate decisions to individual Registrants requesting information on worker exposure and related exposure scenarios that is specific to those operators.

This decision does not imply that the information provided by the Registrant(s) in the registration(s) is in compliance with the REACH requirements. The decision neither prevents ECHA from initiating compliance checks on the dossier(s) of the Registrant(s) at a later stage, nor does it prevent a subsequent decision under the current substance evaluation or a new substance evaluation process once the present substance evaluation has been completed.

[1] The term Registrant(s) is used throughout the decision, irrespective of the number of registrants addressed by the decision.

I. Procedure

Pursuant to Article 45(4) of the REACH Regulation the Competent Authority of The Netherlands has initiated substance evaluation for Tris(methylphenyl) phosphate, CAS No 1330-78-5 (EC No 215-548-8) based on registrations submitted by the Registrant(s) and other relevant and available information and prepared the present decision in accordance with Article 46(1) of the REACH Regulation.

On the basis of an opinion of the ECHA Member State Committee and due to initial grounds for concern relating to (suspected) PBT, wide dispersive use, aggregated tonnage and other (potential neurotoxic effects of the substance in aviation uses), Tris(methylphenyl) phosphate (hereafter referred to as TCP) was included in the Community rolling action plan (CoRAP) for substance evaluation to be evaluated in 2014. The updated CoRAP was published on the ECHA website on 26 March 2014. The Competent Authority of The Netherlands was appointed to carry out the evaluation.

In the course of the evaluation, the evaluating MSCA identified additional concerns regarding high risk characterisation ratios (RCRs).

The evaluating MSCA considered that further information was required to clarify the following concerns: potential neurotoxic effects of the substance in aviation uses and high RCR. Therefore, it prepared a draft decision pursuant to Article 46(1) of the REACH Regulation to request further information. It submitted the draft decision to ECHA on 25 March 2015.

On 4 May 2015 ECHA sent the draft decision to the Registrant(s) and invited them pursuant to Article 50(1) of the REACH Regulation to provide comments within 30 days of the receipt of the draft decision.

By 10 June 2015 ECHA received comments from the Registrant(s) of which it informed the evaluating MSCA without delay. The evaluating MSCA considered the comments received from the Registrant(s).

On basis of this information, Section II was amended. The Statement of Reasons (Section III) was changed accordingly.

Commenting by other MSCAs and ECHA

In accordance with Article 52(1) of the REACH Regulation, on 3 March 2016 the evaluating MSCA notified the Competent Authorities of the other Member States and ECHA of its draft decision and invited them pursuant to Articles 52(2) and 51(2) of the REACH Regulation to submit proposals to amend the draft decision within 30 days of the receipt of the notification.

Subsequently, two Competent Authorities of the Member States and ECHA submitted proposals for amendment to the draft decision.

On 8 April 2016 ECHA notified the Registrant(s) of the proposals for amendment to the draft decision and invited them pursuant to Articles 52(2) and 51(5) of the REACH Regulation to provide comments on those proposals for amendment within 30 days of the receipt of the notification.

The evaluating MSCA reviewed the proposals for amendment received and amended the

draft decision.

Referral to Member State Committee

On 18 April 2016 ECHA referred the draft decision to the Member State Committee.

By 10 May 2016 in accordance to Article 52(2) and Article 51(5), the Registrant(s) provided comments on the proposal(s) for amendment. In addition, the Registrant(s) provided comments on the draft decision. ECHA took the comments on the proposal(s) for amendment of the Registrant(s) into account. ECHA did not take into account the Registrant(s)' comments on the draft decision as they were not related to the proposal(s) for amendment made and are therefore considered outside the scope of Article 52(2) and Article 51(5).

A unanimous agreement of the Member State Committee on the draft decision was reached on 23 May 2016 in a written procedure launched on 13 May 2016.

ECHA took the decision pursuant to Article 51(6) of the REACH Regulation

II. Information required

Pursuant to Article 46(1) of the REACH Regulation the Registrant(s) shall submit the following information using the indicated test methods (in accordance with Article 13(3) and (4) of the REACH Regulation) and the registered substance subject to the present decision:

Toxicity

1. *In vitro* dermal absorption study using test method specified in test method EU B.45 of Regulation (EC) No 440/2008 or OECD 428 using human excised skin with specifications as described in section III. In particular, the study shall be performed using well characterised human skin, an appropriate solvent and doses which are representative of relevant human exposure situations, in line with the recommendation of OECD Guidance Document (GD) 28 on the Conduct of Skin Absorption studies (OECD 2004).

2. 90-day repeated dose neurotoxicity study in the rat, by inhalation nose only (test method EU B.43 of Regulation (EC) No 440/2008 or OECD 424) 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.

Pursuant to Article 46(1) of the REACH Regulation the Registrant(s) shall also submit the following information regarding the registered substance subject to the present decision:

DNEL derivation

3. Justification for the deviation from the ECHA Guidance in the derivation of the DNELs.

Worker exposure

4. An exposure assessment for the exposure scenario of pilots and cabin crew to the registered substance during flights, including a calculation of the inhalation and dermal exposure and calculation of the RCR by combining the RCR (inhalation) and RCR (dermal);

5. Provide all available information on the content and anonymized results of questionnaires, medical and clinical investigations and industrial hygiene assessments among TCP exposed workers, and the study of a possible causal relationship between TCP exposure and neurotoxic complaints, specifically:
   - The questionnaires that were used for health surveillance of TCP exposed workers and a control group of non-TCP exposed workers;
   - The content of the medical and clinical investigations of TCP exposed workers and the control group;
   - The anonymized results of the questionnaires, medical and clinical investigations of both TCP exposed workers and the control group;
   - The methodology and anonymized results of the industrial hygiene assessments;
   - The evaluation of a possible causal relationship between TCP exposure (measurement data and/or estimations) and the results of the questionnaires, medical and clinical investigations.

6. 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 to be made, 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;
   - Details of personal protective equipment within each scenario, including
     - The specifications for all personal protective equipment according to REACH Annex II;
     - The content of both the basic and specific activity training (both information on the substance and instruction how to work safely);
     - The specifications of the engineering controls, i.e. LEV and dilution ventilation, used to protect industrial and professional workers;
   - A copy of the model inputs, modifiers and outputs;
   - A justification for all deviations from the default values as provided in the ECHA guidance or provided in the exposure models;
   - All operational conditions (OCs) or risk management measures (RMMs) shall be quantified to determine whether the risk is adequately controlled;
   - A quantification of the risk, taking into account all RMMs, leading to a final RCR that indicates if the risk to humans is adequately controlled (i.e. the exposure levels do not exceed the appropriate DNEL).

The Registrant(s) shall ensure that any changes made to the exposure assessment as a

consequence of the further data requested are followed up adequately and any necessary amendments made to the risk characterization;

Deadline for submitting the required information

Pursuant to Article 46(2) of the REACH Regulation, the Registrant(s) shall submit to ECHA by **2 August 2018** an update of the registration(s) containing the information required by this decision[2], including robust study summaries and, where relevant, an update of the Chemical Safety Report.

III. Statement of reasons

Toxicity

1. *In vitro* dermal absorption study

Establishing the concern
Information on dermal absorption is required in order to assess the exposure and risk after dermal exposure to the registered substance. The dermal absorption is used to apply route-to-route extrapolation from an oral no observed adverse effect level (NOAEL) identified in the chemical safety report (CSR). By applying default values (irrespective whether 100% or 10% is used as default) for dermal absorption, RCRs > 1 will be derived. According to the CSR, there is dermal exposure of workers and the general public and therefore the risk related to the dermal exposure is of concern. A refinement for the risk related to the dermal exposure is therefore required. The data on dermal absorption of the registered substance was considered to be unreliable to derive a substance specific dermal absorption percentage.

Justification why new information is needed
The human dermal absorption assumption of 2% provided in the registration dossier is considered to be unreliable to predict the absorption of TCP. The human dermal absorption is based on general learnings from animal study by Nomeir and Abou-Donia (1986) and primarily from IH SkinPerm modelling. The Registrant(s) assessed the cat study of Nomeir and Abou-Donia (1986) and concluded a dermal absorption rate ~20% after 24 hours. For the assessment of the human dermal absorption rate the Registrant(s) argues that:
Overall, for this assessment, a mouse/cat dermal penetration ratio of 1 and a mouse/human dermal penetration ratio of 10 are implemented. That is, the mouse and cat are assumed to have similar dermal penetration and the human dermal penetration rate is 10X lower than the mouse [...].Therefore, it is assumed that the human would have approximately 2% absorption of TCP in a 24 hour time period.

No substance-specific information is provided to justify the 10x lower dermal penetration of TCP in human skin compared to cat skin. Therefore, the assessment of the human dermal absorption is considered to be unreliable.

The human skin permeation was also evaluated by the Registrant(s) using a modelling tool, called IH SkinPerm, to estimate the flux for TCP. The Registrant(s) used the estimated flux and modelled exposures associated with each process category (PROC) to assess the mass fraction absorbed relative to the deposition mass. Initially, the Registrant(s) used an observation time of 8 hours leading to absorption fractions ranging from 0.01 to 4.3%

[2] The deadline set by the decision already takes into account the time that registrants may require to agree on who is to perform any required tests and the time that ECHA would require to designate a registrant to carry out the test(s) in the absence of the aforementioned agreement by the registrants (Article 53(1) of the REACH Regulation).

across PROC 1-20. In the commenting phase, the Registrant(s) provided updated absorption fractions using an observation period of 24 hours. These updated absorption fraction range from 0.02 to 11.9% across PROC 1-20. This result is used by the Registrant(s) as a basis for the assumed 2% human dermal absorption. The followed approach by the Registrant(s) is considered unreliable as the estimated absorption fractions are not assessed appropriate.

In order to assess the dermal absorption fraction for the different PROCs, the Registrant(s) have calculated the systematically absorbed mass using IH SkinPerm and subsequently used the ECETOC TRAv3 dermal predicted exposure to generate the absorbed fraction. The Registrant(s) used the ECETOC TRAv3 dermal predicted exposure without the use of RMMs. To assess the dermal absorption fraction using the abovementioned methodology, the **actual** exposure after implementation of the RMMs as described in the relevant exposure scenarios should be used to mimic the anticipated exposure levels in line with the OECD GD 28 Guidance document.

In addition to the information provided in the dossier and the information received during the commenting phase, the study by Hodge and Sterner (1943) in human volunteers was considered. In this study, tri-ortho-cresylphosphate (TOCP) was administered dermally to two volunteers and urine excretion of TOCP was measured. This study was evaluated together with the review by Craig and Barth (1999) in which the data from the Hogde and Sterner study was used to estimate the flux for TOCP. It was concluded that the study by Hogde and Sterner does not have data of sufficient quality to derive a human dermal absorption fraction for TOCP. Key parameters such as quantitative application area, toxicokinetic information regarding the distribution and excretion of TOCP are missing.

According to the CSR, there is dermal exposure of workers and the general public and therefore the risk related to the dermal exposure is of concern. Without the requested information it will not be possible to verify whether there remains an uncontrolled risk with the substance that should be subject to further risk management measures.

What is the request
An *in vitro* dermal absorption test with human excised skin is requested from the Registrant(s). The study shall be performed using well characterised human skin, an appropriate solvent and doses which are representative of relevant human exposure situations. The study shall be conducted according to guidelines EU B.45 or OECD 428 and in line with OECD GD 28 Guidance document. The latter document addresses in more detail important points to consider in order to obtain scientifically valid results.

There are a number of points that require special attention that shall be considered by the Registrant(s):

- Dose, volume, vehicle and contact time with the skin has to mimic in-use conditions.
- The duration has to be at least 24 hours.
- The dose tested should mimic the anticipated exposure levels including the lower and higher end of the expected doses.
- For measurements and calculations of the percentage of absorption the low end of the anticipated exposure shall be used.
- The percentage of absorption shall be used in the route-to-route extrapolation from oral to dermal.

The *in vivo* dermal absorption test was also considered, however, it was concluded that there are at this moment no indications known that the *in vitro* method with the registered substance would provide unreliable data, and moreover the use of human skin is considered

to be appropriate. Furthermore, alternatives for vertebrate testing should be always considered where possible.

The Registrant(s) shall provide a detailed study summary allowing an evaluation of the study.

Information on *in vivo* dermal absorption is needed e.g. to assess the combined dermal and inhalation exposure to the substance. In case the combined exposure exceeds the relevant DNEL, more stringent regulatory risk management measures might be needed to ensure safe use of the substance.

Consideration of Registrants' comments
The Registrant(s) stated in their comments that they feel their approach is more conservative by not reducing the TRAv3 exposure values (e.g. by assigning glove RMMs). The Registrant(s) already noted that an inverse relationship often exists between dermal loading and the fraction of a chemical absorbed. As loading is increased, the fraction of chemical that is absorbed diminishes. However, the fractional absorption factor is not a constant for a given chemical and is typically highest for low dermal loads. Therefore, by not assigning RMMs and using higher exposure values, i.e. higher dermal loading than in the actual occupational setting, the absorption factor under working conditions is underestimated. As the dermal DNEL is determined by a route-to-route extrapolation from an oral study, underestimating the dermal absorption factor will lead to a higher dermal DNEL. This underestimates the actual risks and therefore such an approach should not be regarded as more conservative. Based on the Registrants' comments, the justification for this request was amended.

Conclusion
Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to carry out the following study using the registered substance subject to this decision: *In vitro* dermal absorption study using test method specified in test method EU B.45 of Regulation (EC) No 440/2008 or OECD 428 using human excised skin. In particular, the study shall be performed using well characterised human skin, an appropriate solvent and doses that are representative of relevant human exposure situations, in line with the recommendation of OECD Guidance Document (GD) 28 on the Conduct of Skin Absorption studies (OECD 2004).

2. 90-day repeated dose neurotoxicity study

There has been an ongoing international discussion regarding the possible exposure of pilots and cabin crew to toxic substances in the cabin air during flights. As early as in 1977, articles have been published concerning health problems with cabin crew and pilots. Symptoms include amongst others: dizziness, nausea, tremors, blurred vision, lethargy, disorientation, loss of short time memory and cognitive problems (Montgomery, Wier et al. 1977; Van Netten 1998; Winder, Fonteyn et al. 2002). These symptoms are sometimes summarized as the 'aerotoxic syndrome' (ATS). It has been suggested that ATS has a relation with exposure to tricresyl phosphate (TCP), a potential neurotoxic substance, used as an additive in engine oil for airplanes. In the aviation industry, TCP is added to engine oil for the turbine engines to increase the engine oil's performance at high temperatures. The engine oil containing TCP can contaminate the bleed air (i.e. compressed air that is taken from the compressor stage of the engines), which is used in most aircraft's air-conditioning systems. Indeed, several studies have demonstrated the presence of TCP in the cabin air and on dust wipes (Crump, Harrison et al. 2011; EPAAQ 2011; Rosenberger, Netz-Piepenbrink et al. 2013)

Establishing the concern
There is a concern for possible neurotoxic effects induced by the registered substance, which may occur already at low dose levels. Due to a lack of data covering all aspects of possible neurotoxicity and due to a lack of inhalation studies, it cannot be determined whether the current DNEL covers these potential neurotoxic effects. Since exposure to TCPs via inhalation is considered likely, there is concern that the risks may not be adequately controlled.

TCP is an organophosphate, existing in 10 different isomers, as the cresyl group can be situated at different positions (meta, para or ortho). The tri-ortho-cresylphosphate (TOCP) is known for its neurotoxicity for many decades (Kidd and Langworthy 1933; Henschler 1958; Johnson 1975). Because of its known neurotoxic properties, the tri-ortho-isomeric TCP, together with the mono-ortho and di-ortho isomeric TCP, nowadays only appears as small impurity, or is not present in commercial blends. However, there remains a concern for the potential neurotoxicity of the non-ortho TCP isomers. Organophosphates, as a class of substances, are in general known for their neurotoxic effects and can act via different mechanisms (Marrs 1993). For non-ortho TCP isomers, neurotoxic mechanisms other than the TOCP-mediated organophosphate-induced delayed neuropathy (OPIDN) may contribute to neurotoxic effects. Several studies have described neurological problems in flight crew that may be related to TCP exposure (Cox and Michaelis 2002; Ross 2008; Abou-Donia, Abou-Donia et al. 2013; Hecker, Kincl et al. 2014), however the effect of long-term subclinical exposure to organophosphates is unclear (Abou-Donia 2003; Baker, Cole et al. 2013). Based on the provided information it is possible that non-ortho-TCP isomers contribute to the observed neurotoxicity and a thorough assessment of the neurotoxic effects of TCP is justified.

In addition, there is a concern for the inhalation route of TCP in the form of aerosols. As possible neurotoxic effects cannot be ruled out, inhalation is a specific route of concern due to the possible easier access of the parent substance to the brain prior to being metabolized. The toxicokinetic data provided do not indicate slow absorption in the lung and this is the route of exposure for cabin crew in airplanes. It was noted that the vapour pressure is relatively low, however, the registration dossier shows several exposure scenarios in which the substance is sprayed during work activities. This can result in inhalation exposure in the form of aerosols. The lipophilicity of the registered substance is high. This assumes a direct binding to and diffusion over the cell membranes at the site of deposition. Available literature from drug nebulisation suggests the lung surfactant facilitates the absorption of small lipophilic molecules into the bloodstream through simple diffusion over the cell membrane (Wiedmann, Bhatia et al. 2000; Liao and Wiedmann 2003). The inhalation route of exposure includes the potential direct exposure of the brain to the registered substance through the nose epithelium. The high lipophilicity of the registered substance increases the changes of direct transport over the nose epithelium. The high metabolic capacity of the nose epithelium could result in additional (neuro)toxic metabolites. The formation of such metabolites in the nose is potentially more dangerous than in the liver due to the direct connection to the brain (absence of the blood brain barrier).

Justification why new information is needed
The neurotoxic potency of the registered substance has not been fully examined and therefore additional information is required to address the concern. The current registration of TCP is for the reaction mass of three non-ortho isomeric forms of TCP. The information provided in the registration dossier does not give sufficient information to assess the potential for neurotoxic properties of the non-ortho isomeric forms of TCP.

The provided negative OECD 418 key study (Delayed Neurotoxicity of Organophosphorus Substances Following Acute Exposure) does not give sufficient information. It only detects the specific delayed neurotoxic mechanism by which TOCP exerts its neurotoxicity. The supporting studies can also not address the concern, since they were performed with lubricating oil containing TCP (instead of TCP only), with only a single dose treatment, performed *in vitro* or were aiming to investigate immune responses only. The provided oral (feed and gavage) repeated dose studies in mice and rats performed by the US National Toxicity Program (NTP) do not give sufficient information to address the concern. The study design focusses on the carcinogenic potential of mixed isomers of TCP. Some neurological parameters are incorporated in these studies, both behavioural (grip strength, total activity, startle and paw-lick latency) as well as some specific histopathology aimed at demyelination and axonal degeneration. However, none provides a full neurotoxicity assessment.

The abovementioned studies provide a limited assessment of the neurotoxic potential of non-ortho isomers of TCP. The information in the studies cannot be considered adequate to fully determine the neurotoxic potential of the registered substance, especially toxicity via the inhalation route. No neurotoxic specific data is available after inhalation exposure, nor do the existing studies investigate the effect of non-ortho isomers on behavioral outcomes such as learning and memory. Furthermore, no neurotoxicity specific histopathology is performed.

What is the request
Based on the above mentioned concern and the studies provided by the Registrant(s) information is needed on the neurotoxic properties, other than OPIDN, of the registered substance through the inhalation route. The registered substance as multi-constituent substance has different concentrations/ratios of the three non-ortho TCP isomers. Therefore a representative composition of the registered substance should be tested. If neurotoxicity is observed with the representative test composition and if the risk of different compositions of the registered substance cannot be assessed, ECHA may, in a follow-up to this decision, request to test other compositions of the registered substance to allow for a risk assessment of all possible blends. It is stressed that a comprehensive analytical characterisation of the test composition used is needed conforming to Section IV below.

The OECD has published a specific guideline for neurotoxicity testing in rodents, the OECD 424 test. This test provides a modular testing regime, with adaptations for specific neurotoxic endpoints addressing the specified neurotoxic concerns. The specific neurotoxic concern for the non-ortho isomers of TCP follows from the a-specific neurological effects observed in flight crew and associated with exposure to TCP. The preferred rodent species of the OECD 424 test is the rat and additional functional parameters have to be included to assess cognitive function to determine the effect on memory and learning ability.

To study adverse effects of chemicals on memory, the focus is set primarily on the hippocampus. Several tests are available to study this, one of which is the Morris Water Maze (MWM) test. This test, in which the rodent is guided by spatial cues, investigates different aspects of cognition, i.e. 1) learning (to find a hidden platform) 2) performance: short (working) memory, and 3) retrieval: long term memory. Accuracy of the test is relatively high and 10-15 animals per group suffice to reach statistical levels of significance. Unlike the MWM, avoidance tests (or shuttle box tests) are more general tests to study learning and memory. In active and passive avoidance tasks, also a number of different aspects of cognition can be tested. Avoidance tests are less laborious than MWM. On the other hand, they are less sensitive, i.e. the number of animals reaching the learning criterion (so called: "responders") necessary to test memory in the follow-up, is clearly less compared to MWM. To reach statistical significance, care should be taken that the number

of animals that "learn" ("responders") is high enough to enable the study of memory aspects.

In MWM as well as in avoidances tests, the animals are trained over several days. The equipment for avoidance tests is more automated and –especially the training (learning) sessions are less laborious. Analyses of data are comparable between the tests. Both tests offer the possibility to study different aspects of learning and memory processes. The MWM is more appropriate as it is focused on hippocampus (key structure of learning and memory processes) and avoidance tests are more generic.

The motor activity test, as part of the proposed test, shall include habitation (per test session) and the testing arena shall be divided into a central and peripheral zone. The analyses shall be able to detect possible changes in activity patterns between the central and peripheral zone as inexpensive additional analyses for anxiety or hyperactivity. To detect any delayed occurrence of toxic effects post treatment, a recovery group shall be included in the high dose group. The recovery period shall be at least 1 month and the number of animals in the high dose group should be sufficient to perform all the observation parameters, including the additional function parameters, and histopathology.

Recent findings of elevated levels of autoantibodies to nervous system specific proteins in affected flight crew (Abou-Donia, Abou-Donia et al. 2013) is suggestive of inflammation processes in the brain. In addition, the NTP studies in the dossier showed axonal degeneration of nerves that could not be attributed to the trace amount of TOCP in the test item. Therefore, there is a concern for degeneration and neuro-inflammation. ECHA request the histopathology to 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)

Special attention should be paid to the detection of demyelination and axonal degeneration or loss in the neuropathology.

The Registrant(s) should note that the Guideline recommends a stepwise examination of tissue samples in which sections from the high dose group are first compared with those of the control group. If no neuropathological alterations are observed in the samples from these groups, subsequent analysis is not required. If neuropathological alterations are observed in the high dose group, samples from each of the potentially affected tissues from the intermediate and low dose groups should then be coded and examined sequentially.

The NTP studies in the dossier show a consistent dose-dependent decrease in serum cholinesterase activity. A more relevant assessment of the potential effects of TCP on cholinesterase activity and subsequent neurological effects is the determination of the brain cholinesterase activity. Therefore, brain cholinesterase activity should be determined at the end of exposure and in the recovery group. To limit the use of experimental animals, determination of brain cholinesterase activity in at least three animals per dose group is considered sufficient for the determination of this parameter.

As for the length of the study, a sub chronic (90-day) study is deemed appropriate to address the concern of long-term exposure to TCP. As it is foreseen that individuals can be exposed to TCPs during their entire working life, a sub-chronic toxicity test better reflects the total exposure time. Behavioural effects like impaired memory/learning due to exposure to toxic substances can take some time to develop and a short-term (28-day) toxicity test is therefore not appropriate to reflect the occupational exposure scenarios. Chronic studies (>

1 year) are not deemed proportionate in this case. The preferred route of exposure is inhalation as this is the exposure route of concern.

In case the results of the neurotoxicity study shows evidence of neurotoxicity at low level of exposure, the DNEL may need to be revised as a consequence of that, and more stringent regulatory risk management measures might be needed to ensure safe use of the substance, which also may include more stringent classification.

Consideration of Registrants' comments
In response to the first Draft Decision, as was drafted in May 2015, the Registrant(s) provided several comments. The Registrant(s) opposed the initially requested determination of IgG autoantibodies against various nervous system proteins in sera and of glial fibrillary acidic protein in the brain just before sacrifice. ECHA evaluated the comments and understands that such additional parameters will involve an extra workload for the Registrant(s). Considering the total size of the requested study and the experimental character of the requested markers, the determination of IgG autoantibodies against various proteins was removed from the Draft Decision. The concern for neural degeneration and neuro-inflammation however still remains. Therefore, it is requested to design the histopathology in such way to detect neuro-inflammation and neural degradation. The Draft Decision was amended accordingly.

The Registrant(s) provided comments that the requested behavioural test would not be appropriate with inhalation studies, as factors typical for inhalation toxicity testing would interfere with normal behaviour. In addition, the Registrant(s) argue that alternative tests should be considered for learning and memory because observations of feeding behaviour are included in the OECD 424 to assess the learning and/or memory task. Further, they argue that TCP's potential effect on hunger and general lethargy would need to be considered when choosing behavioural experiments which may rely on food for reinforcement.

ECHA does not agree with the Registrant(s)' statement that inhalation toxicity testing influences the outcome of behavioural tests in such way that it would be considered as a confounding factor by itself. The OECD 424 guideline and guidance document for neurotoxicity testing explicitly states that, based on the expected human use, there may be a need to conduct neurotoxicity testing by the inhalation route. In addition, the OECD 412 and 413 guidelines on inhalation toxicity studies both explicitly state the possibility to combine inhalation studies with neurologic tests.

The MWM is the preferred test to study the effects of the registered substance on learning and memory. However, it is recognized that alternative tests exists that measure learning and memory, such as the T-maze or avoidance tests. The draft decision was amended to provide more information on the different tests to study learning and memory and the Registrant(s) is provided a choice between the MWM and avoidance tests. T-maze is mentioned by the Registrant(s) and is used to study effects on cognition as well. However, the test requires (food) rewards which, in turn, may interfere with the exposure protocol. Moreover, it may be hard to get the animals interested in the reward (takes time). The Registrants note that TCP's potential effects on hunger and general lethargy would need to be considered when choosing behavioural experiments which may rely on food for reinforcement. Considering the above, this test is not suitable for the study proposed.

The Registrant(s) commented that it is unclear if the inhalation route would provide additional data as proposed to an oral dosing regime and the lack of rationale for the study duration. ECHA evaluated the comments and decided not to amend the DD as sufficient

justification is provided for the route and duration of exposure.

Conclusion
Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to carry out the following study using a representative composition of the registered substance subject to this decision: 90-day repeated dose neurotoxicity study in the rat, by inhalation nose only (test method EU B.43 of Regulation (EC) No 440/2008 or OECD 424) with the following adaptations or 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 should 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.

DNEL derivation

3. Justification of the derivation of the DNELs.

Establishing the concern
Information on the assessment factors in the derivation of the DNELs is required in order to enable the evaluating MSCA to assess the risks associated with the use of the registered substance. By applying default values for the remaining interspecies differences, RCRs > 1 will be derived.

Justification why new information is needed
In fulfilling the information requirements listed in section II, where applicable, it might be necessary to compare the exposure estimates with relevant DNELs, in order to identify whether an RCR > 1 is obtained and thus further refinement of the risk characterization is necessary. In this regard, the assessment factors (AF) currently used for deriving DNELs for the registered substance by the Registrant(s) in their registration dossiers do not fully comply with the respective ECHA Guidance document (ECHA Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.8, Version 2.1, November 2012), i.e. the AF for the interspecies difference is considerably smaller than recommended.

The Registrant(s) have adjusted the additional factor of 2.5 for other, remaining, interspecies differences, i.e. toxicokinetic differences not related to metabolic rate (small part) and toxicodynamic differences (larger part). This additional factor is set by the Registrant(s) at 1. "Chronic studies are available in rats and mice; most sensitive species used for point of departure" is given as justification for the adjusted AF. This justification is not sufficient to demonstrate the existence of substance-specific information that shows specific susceptibility differences between species, which are not related to differences in basal metabolic rate.

Sufficient justification is needed to assess the appropriateness of the DNEL. In case sufficient justification cannot be provided, the DNEL may need to be revised as a consequence of that, and more stringent regulatory risk management measures might be needed to ensure safe use of the substance.

What is the request
The Registrant(s) shall provide adequate justification for the deviation from the REACH guidance for assessment factors.

Conclusion
Pursuant to Article 46(1) of the REACH Regulation the Registrant(s) shall submit a justification for the deviation from the ECHA Guidance in the derivation of the DNELs.

Worker exposure

4. Information on the worker exposure of pilots and cabin crew to the registered substance

Establishing the concern
[redacted] There has been an ongoing international discussion regarding the possible inhalation and dermal exposure of pilots and cabin crew to toxic substances in the cabin air during flights and the correlation with reported health problems by cabin crew and pilots, also referred to as 'aerotoxic syndrome' (ATS). It has been suggested that ATS has a relation with exposure to TCP. The engine oil containing TCP can contaminate the bleed air (i.e. compressed air that is taken from the compressor stage of the engines), which is used in most aircraft's air-conditioning systems. Indeed, several studies have demonstrated the presence of TCP in the cabin air and on dust wipes (Crump et al., 2011; EPAAQ, 2011; Hecker et al., 2014). Therefore, there is a concern on a possible risk for pilots and cabin crew during their work and based on the registration information it is not clear if risks are adequately controlled.

Justification why new information is needed
Exposure measurements show that flight crew can be exposed to TCPs in airplanes. The current registration dossiers do not contain an exposure assessment for pilots and cabin crew in airplanes. Supporting studies on exposure-related observations in humans were included in the dossier and based on these reports and studies, the Registrant(s) concluded that TCP is not considered to be present in aircraft cabin air at sufficient levels to cause concern. An exposure scenario with assessment of exposure for TCP in airplanes is required and should be compared to the DNEL to assess whether risks are adequately controlled.

What is the request
The exposure scenario of flight crew exposure in airplanes during flights is missing in the current registration dossiers. This exposure scenario is needed to evaluate if the risks associated with the use are adequately controlled.

In case the exposure for flight crew in airplanes during flights exceeds the DNEL, more stringent regulatory risk management measures might be needed to ensure safe use of the substance.

Consideration of Registrants' comments
The Registrant(s) considers this route of exposure to be accidental and not covered within the scope of risk assessment. However, they acknowledge that the current exposure

scenario (Lubricant professional use) assumes no leakage or exposure into air craft cabins, while literature information indicates that exposure in the cabin may result from "fume events" due to a seal failure. The Registrants agree to consult air craft industry representatives as Downstream Users regarding the scope and inclusion of an exposure assessment of this area via an appropriate means. The Registrant(s) further highlight the supporting measurement data in peer reviewed literature that demonstrate that concentrations fall below detectable levels in the majority of samples and the worst case scenario would lead to an RCR < 1.

The exposure of TCPs in cabin air is not considered to be accidental. Available literature shows that TCPs are generally detected in cabin air, although concentrations are reported to be low, and that this exposure shall be taken into account when demonstrating safe use of the substance. The concern is mainly based on the continuous level exposure to TCP for long term periods, which may results in neurotoxicity in flight crew. The Draft Decision was not amended.

Conclusion
Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to perform an exposure assessment for the exposure scenario of pilots and cabin crew to the registered substance during flights, including a calculation of the inhalation and dermal exposure and calculation of the RCR by combining the RCR (inhalation) and RCR (dermal).

5. Information on the content and anonymized results of questionnaires, medical and clinical investigations and industrial hygiene assessments among TCP exposed workers, and the study of a possible causal relationship between TCP exposure and neurotoxic complaints.

Establishing the concern
There is a concern on the potential neurotoxicity of TCP. Neurotoxic effects are described in pilots and cabin crew. The registered substance is used as an additive in engine oil and hydraulic fluids used in aviation industry. Pilots and cabin crew are exposed to TCP via the aircraft's air-conditioning system through leakage of oils from the motor compartment into the bleed air of the engine under normal operating conditions. Indeed, several studies have demonstrated the presence of TCP in the cabin air and on dust wipes (Crump et al., 2011; EPAAQ, 2011; Hecker et al., 2014). TCP exposed workers in manufacturing and formulation are also exposed to TCP and may also demonstrate neurotoxic effects.

The information in the current registration dossier is not sufficient to conclude on the neurotoxic potential of the registered TCP. The concern is mainly based on the continuous low level exposure to TCP for long term periods, which may results in neurotoxicity in flight crew but also effects workers during manufacturing and formulation of TCP. The current DNEL may not cover these effects and therefore risks may not be adequately controlled.

Justification why new information is needed
In its comment on the initial Draft Decision, the Registrant(s) states that TCP-exposed manufacturing workers have been investigated once a year for several decades. The Registrant(s) also states that industrial hygiene assessments are performed to monitor their workers. Neurological effects of TCP that go undetected in animal studies may be observed in human investigations. The current registration dossiers do not contain any information on questionnaires, medical or clinical investigations and it is not clear whether such investigations were designed to detect neurotoxic effects, despite the statement of the Registrant(s) that no neurotoxic effects were found during health surveillance of TCP exposed workers. Information on these investigations is required to evaluate if they were

sufficiently designed to detect neurotoxic effects and how the results can be interpreted. Further, information is required on the industrial hygiene assessments that are performed to monitor workers. It is not clear whether this means that the Registrant(s) perform TCP exposure measurements on a regular basis, and if these measurements meet internationally accepted guidelines. Inhalation measurements shall be performed according to both EN 689:1995 "workplace atmospheres: guidance for the assessment of exposure to inhalation to chemicals for comparison with limit values and measurement strategy", or the guidance "Testing Compliance with Occupational Exposure Limits for Airborne Substances" (http://www.arbeidshygiene.nl/~uploads/text/file/2011-12%20BOHS-NVvA%20Sampling%20Strategy%20Guidance.pdf) or similar, and EN 482:2012+A1 2015 "workplace exposure; general requirements for the performance of procedures for the measurements of chemical agents".

What is the request
It is requested to provide information on:

- The questionnaires that were used for health surveillance of TCP exposed workers and a control group of non-TCP exposed workers;
- The content of the medical and clinical investigations of TCP exposed workers and the control group;
- The anonymized results of the questionnaires, medical and clinical investigations of both TCP exposed workers and the control group;
- The methodology and anonymized results of the industrial hygiene assessments;
- The evaluation of a possible causal relationship between TCP exposure (measurement data and/or estimations) and the results of the questionnaires, medical and clinical investigations.

In case neurotoxic effects were not evaluated in the questionnaires, medical and clinical investigations, the Registrants may consider adaptation of the methods so that neurotoxic effects can be detected, and provide information of the health surveillance study results.

It is advised to provide an integrated report for all Registrants.

In case the requested data give rise to adaptation of the DNEL, resulting in a RCR > 1, more stringent regulatory risk management measures might be needed to ensure safe use of the substance.

Consideration of Registrants' comments
The Registrant(s) had significant concerns with the initial request for an epidemiological cohort study due to complex methodological and practical challenges. ECHA agrees with the Registrant(s) that an epidemiological cohort study is very complex and that a lot of practical challenges must be resolved. The intention of the request was to ask the Registrant(s) to deliver a cohort of TCP exposed workers, which would be one of the cohorts in a large epidemiologic study, in which neurotoxic effects in humans of TCP will be studied. However, at this moment there are no intentions for such a large epidemiological study at European level. Therefore, the request for obtaining information on neurotoxic effects in humans has been amended and is now based on investigations yearly performed by the Registrant(s).

The Registrant(s) stated in the comments on the initial Draft Decision that TCP exposed manufacturing workers have been investigated once a year for several decades. Both questionnaire, medical investigations as well as clinical investigations (including clinical blood and urine parameters) have been performed. The Registrant(s) states that no neurotoxic effects were found. There is a concern whether the questionnaire, medical and clinical investigations were sufficiently designed to detect neurotoxic effects and how the

relationship between TCP exposure and neurotoxic effects was evaluated.

The Registrant(s) also states that industrial hygiene assessments are performed to monitor their workers. It is not clear to the evaluating MSCA whether this means that the Registrant(s) performs TCP exposure measurements on a regular basis, and if these measurements meet internationally accepted guidelines.

Based on the provided comments, the Draft Decision was amended.

Conclusion
Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to provide all available information on the content and anonymized results of questionnaires, medical and clinical investigations and industrial hygiene assessments among TCP exposed workers, and the study of a possible causal relationship between TCP exposure and neurotoxic complaints, specifically:

- The questionnaires that were used for health surveillance of TCP exposed workers and a control group of non-TCP exposed workers;
- The content of the medical and clinical investigations of TCP exposed workers and the control group;
- The anonymized results of the questionnaires, medical and clinical investigations of both TCP exposed workers and the control group;
- The methodology and anonymized results of the industrial hygiene assessments;

The evaluation of a possible causal relationship between TCP exposure (measurement data and/or estimations) and the results of the questionnaires, medical and clinical investigations.

6. 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 to be made

Establishing the concern
The Registrant(s) have conducted many human exposure assessments. Although they have provided some additional exposure information at the request of the evaluating MSCA, there is currently insufficient detail available in the human exposure assessment to come to a conclusion on the adequacy of the RMMs currently in place. Therefore, there is a concern if risks are adequately controlled.

Justification why new information is needed
Based on the current 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 ECHA. Detailed information on the performed exposure assessment will increase the transparency and allows to verify the exposure estimates derived by the Registrants and understand the parameters chosen. This information is needed to determine whether or not appropriate modifiers have been applied.

Further, the values of some parameters seemed to deviate or showed to be different than the default parameters from the Guidance. When using the default parameters, in many cases risks are not controlled (RCR>1). For example:

In ART the default ART value of 75th percentile was used, instead of a 90th percentile as recommended by the Guidance document (ECHA Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.14, version 2.1, November 2012, p.41).

Such deviations are only valid when an acceptable justification is provided.

Furthermore, for several exposure scenarios qualitative risk management measures were made in case the risk was not controlled: PROC 7 in exposure scenarios ES4- IW1 and ES7-IW2 (inhalation) and PROC 11 in exposure scenarios ES5- PW1, ES8- PW2 and ES13-PW3 (inhalation and dermal). The Registrants used standard RMMs ("eight principles of good practice") without quantifying the effect of the measure in those cases. This is not a correct method to control the risk and adequate control is not demonstrated. If the Risk Characterisation shows that, based on the initial ES, risks are not controlled, further refinement is needed.

Further, for dermal exposure estimations local exhaust ventilation was used to control dermal exposure to TCP (PROC 19). PROC 19 describes work without any specific exposure controls other than PPE, so the use of local exhaust ventilation is not valid for this contributing scenario.

What is the request
Detailed information on the exposure assessment on the registered substance for workers is requested. The Registrant(s) are required to update their CSR to include the information requested for each scenario. The detailed information shall include the initial exposure estimation without modifiers, all values for the parameters used and details on the reduction factors of the RMMs and shall be sufficient to verify the estimated exposure concentrations. Detailed specifications of the personal protection equipment shall be provided:

- For skin protection: the type of material and its thickness, and the typical or minimum breakthrough times of the glove material. In addition, dermal exposure heavily depends on the type of training of the operators (no, basic or specific activity training). The Registrant(s) shall provide the specifications of personal protection equipment and of the content of training.
- For respiratory protection: the adequate mask and the proper purifying element.

Default parameters as provided in the ECHA Guidance shall be used, however, any deviations may be used if they can be sufficiently justified. For all exposure scenarios, the final RCR shall be calculated, taking into account all reduction factors, and determined if the risk to humans is adequately controlled. Further refinement is needed if the Risk Characterisation shows that risks are not controlled. In a second iteration, information at any point of the assessment cycle can be modified. Such iterations must be realistic to the extent that the introduction of operational conditions (OC) and/or risk management measures (RMMs) can be implemented in practice. All OCs or RMMs should be quantified to determine whether the risk is adequately controlled.

In case the requested data give rise to adaptation of the DNEL, resulting in a RCR > 1, more stringent regulatory risk management measures might be needed to ensure safe use of the substance.

Conclusion
Pursuant to Article 46(1) of the REACH Regulation the Registrant(s) shall submit, in the form of an updated Chemical Safety Report (CSR) using the specified approaches where applicable, detailed information on worker exposure is required for all scenarios to allow an assessment of the adequacy of the risk management measures in place for the registered substance to be made, 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;
- Details of personal protective equipment within each scenario, including
  - The specifications for all personal protective equipment according to REACH Annex II;
  - The content of both the basic and specific activity training (both information on the substance and instruction how to work safely);
  - The specifications of the engineering controls, i.e. LEV and dilution ventilation, used to protect industrial and professional workers.
- A copy of the model inputs, modifiers and outputs;
- A justification for all deviations from the default values as provided in the ECHA guidance or provided in the exposure models;
- All OCs or RMMs should be quantified to determine whether the risk is adequately controlled;
- A quantification of the risk, taking into account all RMMs, leading to a final RCR that indicates if the risk to humans is adequately controlled (i.e. the exposure levels do not exceed the appropriate DNEL).

The Registrant(s) should ensure that any changes made to the exposure assessment as a consequence of the further data requested are carried through and any necessary amendments made to the risk characterization.

IV. Adequate identification of the composition of the tested material

In relation to the required experimental studies, the sample of the substance to be used shall have a composition that is within the specifications of the substance composition that are given by all Registrant(s). It is the responsibility of all the Registrant(s) to agree on the tested material to be subjected to the tests subject to this decision and to document the necessary information on composition of the test material. The substance identity information of the registered substance and of the sample tested must enable the evaluating MSCA and ECHA to confirm the relevance of the testing for the substance subject to substance evaluation. Finally, the test(s) must be shared by the Registrant(s).

V. Avoidance of unnecessary testing by data- and cost-sharing

In relation to the experimental studies the legal text foresees the sharing of information and costs between Registrant(s) (Article 53 of the REACH Regulation). Registrant(s) are therefore required to make every effort to reach an agreement regarding each experimental study for every endpoint as to who is to carry out the study on behalf of the other Registrant(s) and to inform ECHA accordingly within 90 days from the date of this decision under Article 53(1) of the REACH Regulation. This information should be submitted to ECHA using the following form stating the decision number above at:
https://comments.echa.europa.eu/comments_cms/SEDraftDecisionComments.aspx

Further advice can be found at http://echa.europa.eu/datasharing_en.asp.

If ECHA is not informed of such agreement within 90 days, it will designate one of the Registrants to perform the studies on behalf of all of them.

VI. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Articles 52(2) and 51(8) of the REACH Regulation. Such an appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on the ECHA's internet page at http://www.echa.europa.eu/regulations/appeals. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

Authorised[3] by Claudio Carlon Head of Unit, Evaluation 2, on behalf of Leena Ylä-Mononen, Director of Evaluation

Annex: List of registration numbers for the addressees of this decision. This annex is confidential and not included in the public version of this decision.

[3] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

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