EUROPEAN CHEMICALS AGENCY

Helsinki, 12 June 2020

Addressees
Registrants of JS_78-40-0_TEP as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
18/06/2018

Registered substance subject to this decision ("the Substance")
Substance name: Triethyl phosphate
EC number: 201-114-5
CAS number: 78-40-0

Decision number: Please refer to the REACH-IT message which delivered this communication (in format CCH-D-XXXXXXXXXX-XX-XX/D)

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by the deadline of ***19 September 2022***.

Requested information must be generated using the Substance unless otherwise specified.

A. Information required from all the Registrants subject to Annex X of REACH

1. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) by oral route, in rats, specified as follows:**
   - **Ten weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce systemic toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity);**
   - **Cohort 1B (Reproductive toxicity) without extension to mate the Cohort 1B animals to produce the F2 generation which shall be followed to weaning;**
   - **Cohorts 2A and 2B (Developmental neurotoxicity);**

   You must report the study performed according to the above specifications. Any expansion of the study must be scientifically justified.

Reasons for the request(s) are explained in the following appendix:

- Appendix entitled "Reasons to request information required under Annex X of REACH".

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you, and in accordance with Articles 10(a) and 12(1) of REACH:

- the information specified in Annexes VII to X to REACH, for registration at more than

1000 tpa.

You are only required to share the costs of information that you must submit to fulfil your information requirements.

How to comply with your information requirements

To comply with your information requirements you must submit the information requested by this decision in an updated registration dossier by the deadline indicated above. You must also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information.

You must follow the general testing and reporting requirements provided under the Appendix entitled "Requirements to fulfil when conducting and reporting new tests for REACH purposes". In addition, you should follow the general recommendations provided under the Appendix entitled "General recommendations when conducting and reporting new tests for REACH purposes". For references used in this decision, please consult the Appendix entitled "List of references".

Appeal

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

Failure to comply

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

Authorised[1] under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

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

Appendix A: Reasons to request information required under Annex X of REACH

1. Extended one-generation reproductive toxicity study

The basic test design of an Extended one-generation reproductive toxicity (EOGRT) study (OECD TG 443) is a standard information requirement under Annex X to REACH. Furthermore Column 2 of Section 8.7.3. defines when the study design needs to be expanded.

You provided the following waiving statement:

"No reliable multi-generation study is available for triethyl phosphate. In an early investigation ([redacted], 1968) not following GLP or Guideline with only 5 rats/sex and dose the effects of triethyl phosphate in food were investigated. The animals were treated for 92 days prior to mating and during mating and weaning. This study is of low significance due to the low number of animals per dose group, the absence of analytics and definition of doses, insufficient parameters investigated and inadequate description of results. However, taking into account Guideline-compliant subacute and subchronic repeated dose toxicity studies in rats and Guideline-compliant developmental toxicity studies in rats and rabbits with triethyl phosphate there is no indication of a potential to interfere with reproduction. The results of the studies with special emphasis on relevant parameters for reproduction toxicity are reported here:

1) In a 28 day repeated dose toxicity study ([redacted], 1992) the test item was given via oral gavage in doses of 0, 10, 100, and 1000 mg/kg bw/day to 5 male and 5 female Wistar rats per dose group. This study followed OECD TG 407 and was conducted in compliance with GLP. […]The NOEL for effects on reproductive organs can be established with > 1000 mg/kg bw/day, the highest dose in this 28 day study.

2) In the 90 day repeated dose toxicity study ([redacted] 2017) the test item was given via oral gavage in doses of 0, 60, 200 or 700 mg/kg bw/day to 10 male and 10 female Wistar rats per dose group. This study followed OECD TG 408 and was conducted in compliance with GLP. […] The NOEL for effects on reproductive organs is established with > 700 mg/kg bw/day, the highest dose in 90 day study.

3) In a prenatal developmental toxicity study in rats ([redacted], 1995) groups of 25 inseminated Wistar rats each were treated daily orally by gavage with triethyl phosphate from day 6 to day 15 of gestation in doses of 0, 25, 125 or 625 mg/kg body weight, respectively. The fetuses were delivered by cesarian section on day 20 of gestation. This study followed OECD TG 414 of that time and was conducted in compliance with GLP. […] The NOAEL for developmental/reproductive toxicity was 625 mg/kg bw/day in this study.

4) In a prenatal developmental toxicity study in rabbits [redacted], 2007) groups of 22 pregnant New Zealand rabbits per dose group were treated by oral gavage from Days 6 to 28 of gestation at doses of 0, 30, 80 and 250 mg/kg bw/day. The fetuses were delivered by cesarian section on day 29 of gestation. This study followed OECD TG 414 and was conducted in compliance with GLP. […] Based on the results in this prenatal developmental toxicity study in rabbits the developmental NOAEL was determined to be at least 250 mg/kg bw/day. In summary, based on the available repeated dose and developmental toxicity studies there is no indication of potential interferene of the substance with reproduction. Therefore, further testing for reproductive toxicity is not of priority."

As you have provided four sources of information ECHA has interpreted your adaptation and evaluated it according to Annex XI, Section 1.2 of REACH (weight of evidence).

In support of your adaptation, you have provided the following sources of information:

1. A 28 day repeated dose toxicity study with the substance conducted in accordance with OECD TG 407 ([redacted], 1992)
2. A 90-day repeated dose toxicity study with the Substance conducted in accordance with OECD TG 408 study ([redacted], 2017)
3. A prenatal developmental toxicity study in rats ([redacted], 1995) provided in the Developmental toxicity endpoint in the IUCLID dossier
4. A prenatal developmental toxicity study in rabbits ([redacted] 2007) provided in the Developmental toxicity endpoint in the IUCLID dossier

Furthermore, you provided a multi-generation study ([redacted], 1968) with triethyl phosphate (reliability 4, no guideline, no GLP) in your dossier but you do not refer to this study in your adaptation.

Based on the presented sources of information, you argue that the available data gives sufficient information to conclude on the reproductive toxicity because: *"based on the available repeated dose and developmental toxicity studies there is no indication of potential interference of the substance with reproduction.* " and conclude that "*Therefore, further testing for reproductive toxicity is not of priority.*"

Annex XI, Section 1.2 states that there may be sufficient weight of evidence from several independent sources of information leading to assumption/conclusion that a substance has or has not a particular dangerous (hazardous) property, while information from a single source alone is insufficient to support this notion.

According to ECHA Guidance R.4, a weight of evidence adaptation involves an assessment of the relative values/weights of the different sources of information submitted. The weight given is based on the reliability of the data, consistency of results/data, nature and severity of effects, and relevance and coverage of the information for the given regulatory endpoint. Subsequently, relevance, reliability, coverage, consistency and results of these sources of information must be balanced in order to decide whether they together provide sufficient weight to conclude that the Substance has or has not the (dangerous) property investigated by the required study.

Annex XI, section 1.2 requires that adequate and reliable documentation is provided to describe your weight of evidence approach.

While you have listed in your waiver various studies tackling some reproductive toxicity aspects/parameters to justify you adaptation, you have not included a justification with an assessment, integration and weighing of the individual sources of information for relevance, reliability, coverage, consistency and results, and subsequently decided whether they together provide sufficient weight to conclude that the Substance has or has not the dangerous property investigated by the required study.

Irrespective of the above mentioned deficiencies on the documentation, which in itself could lead to the rejection of the adaptation, ECHA has assessed the provided sources of information.

Relevant information that can be used to support weight of evidence adaptation for the information requirement of Section 8.7.3 at Annex X includes similar information that is

produced by the OECD TG 443 design as specified in this decision. At a general level, this includes information on i) sexual function and fertility, ii) toxicity to offspring, iii) systemic toxicity, - and iv) if column 2 triggers are met, also information on sexual function and fertility of the offspring, developmental neurotoxicity and/or developmental immunotoxicity.

i. Sexual function and fertility

Sexual function and fertility on both sexes includes information on mating, fertility, gestation, parturition, lactation, organ weights and histopathology of reproductive organs and tissues, oestrous cyclicity, sperm count, sperm analysis, hormone levels, litter sizes, nursing performance and other potential aspects on sexual function and fertility.

Sources 1. and 2. (the OECD TG 407 and 408 studies) provide relevant information on organ weights and histopathology of reproductive organs. The sources of information 3. and 4. (the pre-natal developmental toxicity studies), provide relevant information on sexual function and fertility in parental animals only for one aspect, maintenance of pregnancy.

Information on sexual function and fertility (functional fertility and histopathology of reproductive organs and tissues) must be investigated in parental P0 animals as indicated in OECD TG 443 after at least ten weeks premating exposure duration if extension of Cohort 1B is not included[2].

In the case of your Substance, the conditions to include the extension of Cohort 1B are currently not met. The sources of information 1. and 2. inform on organ weights and histopathology for reproductive organs without mating and functional fertility data. The other sources, 3. and 4., do not investigate maintenance of pregnancy without mating and most aspects of sexual function and fertility.

None of the sources of information investigate functional fertility in the P0 generation with sufficient premating exposure duration to ensure the coverage of full spermatogenesis and folliculogenesis before mating.

In the absence of information on the functional fertility after exposure to the Substance over a pre-mating period of 10 weeks, no reliable conclusion can be drawn on sexual function and fertility as required by the information requirement.

ii. Toxicity to the offspring

Toxicity to offspring includes information on deaths before, during or after birth, growth, sexual maturity, oestrous cyclicity, histopathology of reproductive organs in adulthood and other potential aspects on toxicity to offspring.

The sources of information 3. and 4. provide relevant information on toxicity to the offspring.

However, they provide information on toxicity to the offspring *in utero*.

Information provided on toxicity to offspring is limited and does not cover all relevant and essential aspects as defined above. None of the sources of information informs on toxicity to the offspring up to adulthood. Therefore, no conclusion can be drawn on toxicity to the offspring as required by the information requirement.

[2] ECHA Guidance R.7a, Section R.7.6

iii. Systemic toxicity

Systemic toxicity includes information on clinical signs, survival, body weights, food consumption, haematology, clinical chemistry, organ weights and histopathology of non-reproductive organs and other potential aspects on systemic toxicity in both the parental and F1 generations.

All sources of information (1. to 4.) provide relevant information on systemic toxicity.

Sources of information 1. and 2. provide information on systemic toxicity, especially haematology, clinical chemistry and organ weight and histopathology of non-reproductive organs from up to 10 adult animals/sex/group. Sources 3. and 4. include very limited investigations in dams.

Therefore, the information provided on systemic toxicity is limited and does not cover all relevant and essential aspects as defined above. In particular, there is no information on systemic toxicity from the F1 generation, such as clinical signs, body weights, haematology, clinical chemistry, organs weights and histopathology of non-reproductive organs in adulthood. Therefore, the information on systemic toxicity does not cover the required aspect on systemic toxicity and no conclusions on systemic toxicity and its relationship with reproductive toxicity can be made.

iv. Information on triggered investigations

If column 2 triggers are met, information from sexual function and fertility of the offspring, developmental toxicity in F2 generation, developmental neurotoxicity and/or developmental immunotoxicity are relevant. Developmental toxicity includes assessment of neurotoxicity (auditory startle test, functional observation battery, motor activity), information on neurohistopathology and other potential aspects on developmental neurotoxicity. Developmental immunotoxicity includes splenic lymphocyte subpopulation analysis, T-cell dependant antibody response assay, assessment of imune organs and other potential asepcts of developmental immunotoxicity.

As explained below under the specifications for the study design, for the Substance, column 2 triggers are met for developmental neurotoxicity. However, you have not addressed the key elements of developmental neurotoxicity.

Therefore, the available information does not cover developmental neurotoxicity at all and no conclusion on developmental neurotoxicity can be made.

Conclusion on your Weight of Evidence adaptation

Taken together, the sources of information as indicated above provide relevant but limited information on:

- sexual function and fertility on the parental P0 generation, but it does not cover the functional fertility, except for the maintenance of pregnancy.
- toxicity to offspring, lacking information on relevant life stages of the F1 generation (post-natal period up to adulthood)
- systemic toxicity, but not covering relevant life stages of the F1 generation (post-natal period up to adulthood).

Therefore, a significant amount of essential investigations that would inform on sexual function and fertility, toxicity to offspring and systemic toxicity are limited or totally lacking. There is no information provided which informs on developmental neurotoxicity.

It is thus, not possible to conclude, based on any source of information alone or considered together, whether your Substance has or has not the particular dangerous properties foreseen to be investigated in an OECD TG 443 study with the design as specified in this decision. Therefore, your adaptation is rejected and the information requirement is not fulfilled.

Based on the above, the information you provided does not fulfil the information requirement.

The specifications for the study design

Premating exposure duration and dose-level setting

The length of premating exposure period must be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

Ten weeks premating exposure duration is required to obtain results adequate for classification and labelling and /or risk assessment. There is no substance specific information in the dossier supporting shorter premating exposure duration.[2]

Therefore, the requested premating exposure duration is at least ten weeks.

In order to be compliant and not to be rejected due to too low dose levels, the highest dose level shall aim to induce systemic toxicity, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and systemic toxicity. The dose level selection should be based upon the fertility effects. A descending sequence of dose levels should be selected in order to demonstrate any dose-related effect and to establish NOAELs.

If there is no relevant data to be used for dose level setting, it is recommended that range-finding results are reported with the main study.

You have to provide a justification with your study results that demonstrates that the dose level selection meets the conditions described above.

Cohorts 1A and 1B

Cohorts 1A and 1B belong to the basic study design and must be included.

Cohorts 2A and 2B

The developmental neurotoxicity Cohorts 2A and 2B need to be conducted in case of a particular concern on (developmental) neurotoxicity.

Existing information on the Substance itself ([redacted] (2017 – OECD TG 408); [redacted] (1968); [redacted] (1971)) derived from available *in vivo* studies, show evidence of neurotoxicity.

The Substance showed the following functional findings, although without supportive clinical signs or neural histopathology, at not markedly toxic dose levels in the OECD TG 408 study: *"In 700 mg/kg females, total movement levels were reduced in a statistically significant manner when compared to controls", "Grip strength was unaffected in males, however in*

females, foregrip strength in 60 and 700 mg/kg groups, and hindgrip strength in the 700 mg/kg group were reduced in a statistically significant manner."

In addition, the substance inhibited significantly cholinesterase in blood after 100 days of exposure in all treated groups of males and in females *"a progressive decrease"* with increasing dose levels was observed ([redacted] 1968)..

Furthermore, in the provided OECD 408 study there are histopathological findings (organ weight not reported) in thyroid. There is an increased liver weight and associated histopathological findings in the high dose males, but the thyroid hypertrophy is observed already at lower doses. Therefore, a thyroid effect cannot be excluded.

The Substance itself shows signs of thyroid toxicity, reduced total movement levels and reduced grip strength and signs of cholinesterase inhibition which is considered a specific mechanism of action with an association to developmental neurotoxicity.

Therefore, the developmental neurotoxicity Cohorts 2A and 2B need to be conducted.

Species and route selection

The study must be performed in rats with oral[3] administration.

Further expansion of the study design

The conditions to include the extension of Cohort 1B are currently not met. Furthermore, no triggers for the inclusion of Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including the extension of Cohort 1B, and/or Cohort 3 if relevant information becomes available from other studies or during the conduct of this study. Inclusion is justified if the available information meets the criteria and conditions which are described in Column 2, Section 8.7.3., Annex X. You may also expand the study due to other scientific reasons in order to avoid a conduct of a new study. The study design, including any added expansions, must be fully justified and documented. Further detailed guidance on study design and triggers is provided in ECHA Guidance[2].

In your comments you agree to perform the study.

[3] ECHA Guidance R.7a, Section R.7.6.2.3.2.

Appendix B: Requirements to fulfil when conducting and reporting new tests for REACH purposes

A. Test methods, GLP requirements and reporting

1. Under Article 13(3) of REACH, all new data generated as a result of this decision must be conducted according to the test methods laid down in a European Commission Regulation or to international test methods recognised by the Commission or ECHA as being appropriate.

2. Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

3. Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[4].

B. Test material

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

1. Selection of the Test material(s)

   The Test Material used to generate the new data must be selected taking into account the following:
   - the variation in compositions reported by all members of the joint submission,
   - the boundary composition(s) of the Substance,
   - the impact of each constituent/ impurity on the test results for the endpoint to be assessed. For example, if a constituent/ impurity of the Substance is known to have an impact on (eco)toxicity, the selected Test Material must contain that constituent/ impurity.

2. Information on the Test Material needed in the updated dossier
   - You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
   - The reported composition must include all constituents of each Test Material and their concentration values and other parameters relevant for the property to be tested.

This information is needed to assess whether the Test Material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[5].

[4] https://echa.europa.eu/practical-guides
[5] https://echa.europa.eu/manuals

Appendix C: Procedure

This decision does not prevent ECHA from initiating further compliance checks at a later stage on the registrations present.

ECHA followed the procedure detailed in Articles 50 and 51 of REACH.

The compliance check was initiated on 19 August 2019.

ECHA notified you of the draft decision and invited you to provide comments within 30 days of the notification.

ECHA took into account your comments and amended the deadline.

> The deadline indicated in the draft decision to provide the information requested was 18 months from the date of adoption of the decision.
>
> In your comments on the draft decision, you requested an extension of the deadline to 31 months. You justified your request by providing a statement from a CRO indicating the standard timeline and steps needed for completion of the OECD TG 443.
>
> ECHA notes that the EOGRT study can be performed in 18 months. The dose range finding study can also be performed during this time. However, ECHA understands that more time is required for the preparation and reporting of the study.
>
> Therefore, ECHA has partially granted the request and set the deadline to 24 months.

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

Appendix D: List of references - ECHA Guidance[6] and other supporting documents

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 where relevant.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 where relevant.

Read-across assessment framework (RAAF, March 2017)[7]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

Data sharing
Guidance on data-sharing (version 3.1, January 2017), referred to as ECHA Guidance on data sharing in this decision.

OECD Guidance documents[8]

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[6] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[7] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[8] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

Guidance document on transformation/dissolution of metals and metal compounds in aqueous media – No 29, referred to as OECD GD 29.

Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption – No 150, referred to as OECD GD 150.

Guidance Document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test – No 151, referred to as OECD GD 151.

Appendix E: Addressees of this decision and the corresponding information requirements applicable to them

You must provide the information requested in this decision for all REACH Annexes applicable to you.

Registrant Name	Registration number	Highest REACH Annex applicable to you
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

NOTE: Where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.