ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 16 May 2018

Addressee: [redacted]

Decision number: CCH-D-2114407660-58-01/F
Substance name: Methylphosphonic acid, compound with amidinourea (1:1)
EC number: 282-758-4
CAS number: 84402-58-4
Registration number: [redacted]
Submission number: [redacted]
Submission date: 06/07/2017
Registered tonnage band: 100-1000

## DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the REACH Regulation), ECHA requests you to submit information on:

1. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) in rats with the registered substance;**

2. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2., column 2; test method: EU B.31./OECD TG 414) in a second species (rat), oral route with the registered substance;**

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI to the REACH Regulation. To ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective annex, and adequate and reliable documentation.

You have to submit the requested information in an updated registration dossier by **25 May 2020**. You also have to update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2 and advice and further observations are provided in Appendix 3.

### Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals.

Authorised[1] by **Claudio Carlon**, Head of Unit, Evaluation **E2**

[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.

EUROPEAN CHEMICALS AGENCY

**Appendix 1: Reasons**

**1. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.)**

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

A "sub-chronic toxicity study (90 day)" is a standard information requirement as laid down in Annex IX, Section 8.6.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have not provided any study record of a sub-chronic toxicity study (90 day) in the dossier that would meet the information requirement of Annex IX, Section 8.6.2.

In the technical dossier you have provided the following study records for this endpoint:

i. Key study: [redacted] ([redacted] 2012), according to OECD TG 407 (with deviations), GLP compliant; and
ii. Supporting study: [redacted] ([redacted] 2011), not GLP compliant.

However, the studies above do not provide the information required by Annex IX, Section 8.6.2., because exposure duration is less than 90 days and the number of animals per dose group is significantly lower than in the 90 day sub-chronic toxicity study (OECD TG 408). Therefore, the sensitivity of a 28-day study (and even more a 7-day study) is much lower than that of a 90-day study.

Additionally, while you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex IX, Section 8.6.2., column 2, 4th indent, where the 90-day study does not need to be conducted if *"(i) the substance is unreactive, (ii) insoluble (iii) and not inhalable and (iv) there is no evidence of absorption and (v) no evidence of toxicity in 28-day 'limit test', particularly if such a pattern is coupled with limited human exposure."*

ECHA notes that for the specific adaptation set in Annex IX, Section 8.6.2., column 2, 4th indent, to be fulfilled, all the cumulative conditions (i) to (iv) need to be met.

You provided the following justification: *"a sub-chronic toxicity study (90 days) by the oral route does not need to be conducted because the substance is unreactive, insoluble and not inhalable and there is no evidence of absorption and (v) no evidence of toxicity in a 28-day limit test and human exposure is limited"*. However, ECHA notes that your adaptation does not meet the specific rules for adaptation of Annex IX, Section 8.6.2., column 2, 4th indent, as noted in the following considerations:

i. The water solubility of your substance is reported as >470 g/L at 20°C, pH ca 2.8, that is calculated from the [redacted]% aqueous solution that is manufactured and used. The substance shows (some) solubility in octanol (< 1g/L). Thus the substance is soluble. This solubility in octanol, and the octanol-water partition coefficient for this substance indicates the potential for absorption of the substance. Therefore, the available information for the substance contradicts your justification and does not meet the criteria in the specific rule for adaptation for this endpoint. Furthermore, this information is in itself not sufficient to demonstrate lack of absorption or dissolution of the substance in the gastrointestinal tract following oral exposure.

ii. You also state that the substance is inhalable since it is manufactured as a [redacted]% aqueous solution ([redacted]) and has a low vapour pressure (0.0011 Pa at 25°C).

iii. Your justification states that there is no evidence of absorption. Nevertheless, you state in the technical dossier: *"there is evidence from available toxicity studies and physico-chemical properties that MPAAU was absorbed and distributed systemically when administered orally. Short-term toxicity studies with relatively large doses of MPAAU suggest that absorbed MPAAU and potential metabolites are rapidly eliminated without impact to the test animals. MPAAU and its potential metabolites do not present a genotoxic hazard and do not cause significant local or systemic toxicity in animals."* In addition you indicate an absorption rate of 100% oral, under the toxicokinetics endpoint in IUCLID. There is thus evidence for absorption of the substance.

iv. Your justification also refers to the lack of toxicity in the available short-term toxicity (28-day) study. ECHA notes, however, that although there is no evidence of systemic toxicity in the 28-day study, some toxic effects have been noted in the 7-day study when using higher doses: transient reductions in growth and feed intake, and possibly with a tendency toward increased relative kidney weight. Moreover, signs of maternal toxicity were noted in the high-dose group of the OECD TG 414 study in rabbits, that included mortality, conditional decline, blood around the perineum and/or in the cage, growth retardation and reduced feed intake. As your justification argument does not bring any additional elements compared to the specific rule for adaptation noted above, the lack of evidence for toxicity or absorption in the 28-day study is not sufficient information in a weight of evidence argument. Moreover, ECHA notes that according to the information provided in the technical dossier there is limited human exposure (PROCs 3, 8b for manufacture; PROCs 5, 8b, 9, for formulation and PROC 13 for uses at industrial sites), thus there is potential worker exposure.

Hence, conditions (i), (ii), (iii) and (iv) of Annex IX, Section 8.6.2., column 2, 4th indent, are not met. Therefore, your adaptation of the information requirement is rejected.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA has evaluated the most appropriate route of administration for the study. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA considers that the oral route - which is the preferred one as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.5.4.3 - is the most appropriate route of administration. More specifically, the substance is a liquid of very low vapour pressure and no uses with spray application are reported that could potentially lead to aerosols of inhalable size. Hence, the test shall be performed by the oral route using the test method EU B.26./OECD TG 408.

According to the test method EU B.26./OECD TG 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Repeated dose 90-day oral toxicity study (test method: EU B.26./OECD TG 408) in rats.

*Notes for your consideration*

ECHA notes that a revised version of OECD TG 408 may be adopted later on this year by the OECD. This revised version contains enhancements of certain endocrine disrupting relevant parameters. After the adoption of the revised version of the OECD TG 408 you should test in accordance with that version of the guideline as published on the OECD website for adopted test guidelines (https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788).
Even if you start testing before the guideline is published, it is appropriate to consider including these endocrine-sensitive parameters in your testing protocol in accordance with the proposed revised version of the draft guideline (see http://www.oecd.org/env/ehs/testing/section4-health-effects.htm).

**2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2., column 2) in a second species**

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to IX to the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

A "pre-natal developmental toxicity study" (test method EU B.31./OECD TG 414) for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. Annex IX, Section 8.7.2., column 2 provides that the decision on the need to perform a pre-natal developmental toxicity study on a second species at a tonnage level of 100 to 1000 tonnes per year should be based on the outcome of the first test and all other relevant and available data. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet these information requirements.

The technical dossier contains a pre-natal developmental toxicity study with rabbits by the oral route. This study fulfils the standard information requirement for a pre-natal developmental toxicity study in a first species (Annex IX, Section 8.7.2.).

ECHA has reviewed the findings from the study you submitted and considers that the results of the 1st PNDT in rabbits indicate a concern for developmental toxicity, which would trigger the need to perform a PNDT study in a second species because:

i. One foetus in the mid-dose group (from dam no.105) showed a malformed head (namely agenesis of all soft tissues and all skull bones, except tongue and lower jaw) at non-maternal toxic level.
ii. One foetus, from a high-dose dam (no. 149) with an early delivery, showed absence of the cranial vault (agenesis of frontal, parietal and supra occipital skull bones) at a dose level with severe maternal toxicity.

iii. Skeletal retardations in ossification were observed in the mid and high dose groups;
iv. Foetal weights were decreased in the mid- and high-dose group.

ECHA considers that the two foetuses showing severe head malformations indicate a concern for developmental toxicity, although in low numbers. The concern is supported by the other foetal findings both at mid and high dose levels and the fact that other malformed foetuses may have died in utero.

Furthermore, ECHA notes your statement that in previous studies the laboratory has had low incidence of acephaly with this strain of rabbits.

In your comments on the draft decision you stated that a prenatal developmental toxicity study in a second species is not necessary because: *"no concern indicated in 1st species (rabbit) and lack of added value for a PNDT study in rat"*.

Regarding ancephaly, you present in your comments tables with historical control data to prove that the *"finding is commonly observed in this rabbit strain"*. As explained below ECHA does not consider it as a common finding.

Furthermore you address the four concerns raised by ECHA in the draft decision.

i. You state that a single occurrence with a malformed head is not significant. ECHA responds that a single occurrence with a malformed head at a mid-dose level should be considered together with effects seen at the high dose level and together with the other signs of developmental toxicity. In addition, increased post-implantation loss (at the high dose level), a delayed ossification and a reduction in foetal body weight (at the mid and high dose levels) were also detected. You also provided two tables (Annex 1) in your comments and you state that the *"finding is commonly observed in this rabbit strain"*. ECHA however considers that based on the historical control data provided in the table it is unclear how you came to your conclusion that malformed head would be a common finding among the historical controls since among 1104 control foetuses in six separate studies, one control foetus had acephaly. Regarding the historical control data from literature, ECHA considers that the paper by [redacted] (2012) you provided in your comments indicates that there is some variation between different laboratories in the incidence of foetuses with malformations. ECHA however considers that the incidence is very low and that it cannot be considered as a common finding.
ii. You state that the absence of skull bones was observed in one foetus in the high dose group, and that there was maternal toxicity in this dose. However, ECHA reminds that all findings need to be considered together, both from the mid and high levels, i.e. malformations, variations, an increase in post-implantation loss and a reduction in foetal body weight. ECHA considers that the observed developmental effects cannot be explained by the maternal toxicity and, thus they raise a concern that motivates further evaluation. Furthermore, ECHA notes that the Appendix I to your comments – Triskelion statement on the rabbit PNDT study does not provide any new information that is not already in the dossier covered in this decision.
iii. and iv. You state that skeletal retardations in ossification and foetal weight decrease are not relevant for developmental toxicity and that the first one is secondary to the lower foetal weight. ECHA considers, however, that the malformations discussed above demonstrate a concern for developmental effects. This concern is supported by the other findings both at mid and high dose levels

(post-implantation loss, reduced foetal weights and reduced skeletal ossification). Whether or not the retardations in ossification are considered secondary to the lower foetal weight, it does not remove the concern for developmental toxicity. You did not provide any supporting evidence that these findings would not be of relevance for developmental toxicity when occurring together with other developmental findings. Finally, ECHA emphasises that a decreased foetal weight may precede malformations at higher doses. Delayed ossification and reduced foetal weight are not proposed to be the only findings raising the concern for developmental toxicity, but they are considered to support the concern, especially as observed also at the mid dose.

ECHA further notes that in the review paper by [redacted] (2016) you provided in your comments it was concluded that "*delayed ossification is considered to be principally reversible, provided that the cartilage anlagen are developed*". The authors also concluded that the time needed for catch-up of delayed ossification varied considerably between the studies. The authors also pointed to another study in which reduced ossification could not be attributed to body weight effects only. Thus, it is important to consider whether the reduced foetal body weight and skeletal ossification are secondary to maternal toxicity or not. ECHA considers that there is no such link at the mid dose level in this case.

In addition to the four concerns discussed above, you also indicate in your comments that a) there is absence of adverse effects in the rat repeated dose toxicity study (28-day study), making the rabbit a more sensitive species; b) the effects in the rabbit PNDT as having low toxicological significance; c) the effects related to reduced feed consumption of low human relevance; and d) there is negligible exposure of humans.

ECHA notes that

a) Regarding the absence of adverse effects in rats, ECHA notes that although there is no evidence of systemic toxicity in the 28-d study, the dossier contains a 7-day study in rats which shows some effects ("*reductions in growth and feed intake, and possibly a tendency toward increased relative kidney weight*").

   Regarding the statement in your comments that "*the rabbit is the more sensitive species*" ECHA considers that it is not scientifically justified to compare results from adult non-pregnant rats with results from pregnant rabbits to determine the most sensitive species. Based on the information available in the dossier and in your comments it is not possible to conclude which species is the most sensitive with respect to developmental toxicity.

b) Regarding the findings in the rabbit PNDT ECHA refers to the response above.

c) You indicate that the reduced feed consumption in rabbits is "*probably associated with digestive disturbances*" and that the observed effects are due to that cause. However, you have not provided any evidence to support your claim.
d) In your comments you also state that "*there is negligible exposure of humans*" and you provide some route considerations. ECHA notes that further testing is not dependent on exposure levels but aims at hazard identification. Further, the argument provided does not provide adequate justification or documentation that the criteria set forth under Section 3 of Annex XI to the REACH Regulation would be met.

Consequently, the results of the existing rabbit OECD TG 414 raise a concern for developmental toxicity, which motivates further evaluation. A PNDT study in a second

species (rat) will address the concern seen in the test results of the PNDT first species and hence it has added value.

ECHA considers that your arguments provided do not allow to conclude that there is no further concern for developmental toxicity or that the rat is not an appropriate species.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement because the available data contain triggers for prenatal developmental toxicity in a second species. Consequently there is an information gap and it is necessary to provide information for this endpoint.

The test in the first species was carried out with rabbits. According to the test method EU B.31./OECD TG 414, the rat is the preferred rodent species and the rabbit is the preferred non-rodent species. On the basis of this default assumption, ECHA considers that the test should be performed with rats as a second species.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a second species (rat) by the oral route.

*Notes for your consideration*

ECHA notes that a revised version of OECD TG 414 may be adopted later on this year by the OECD. This revised version contains enhancements of certain endocrine disrupting relevant parameters. After the adoption of the revised version of the OECD TG 408 you should test in accordance with that version of the guideline as published on the OECD website for adopted test guidelines (https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals-section-4-health-effects_20745788).

Even if you start testing before the guideline is published, it is appropriate to consider including these endocrine-sensitive parameters in your testing protocol in accordance with the proposed revised version of the draft guideline (see http://www.oecd.org/env/ehs/testing/section4-health-effects.htm).

## Appendix 2: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 16 August 2017.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

ECHA notified you of the draft decision and invited you to provide comments.

ECHA took into account your comments and did not amend the request(s).

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

As no amendments were proposed, ECHA took the decision according to Article 51(3) of the REACH Regulation.

**Appendix 3: Further information, observations and technical guidance**

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

2. Failure to comply with the requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

3. In relation to the information required by the present decision, the sample of the substance used for the new tests must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants.

It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new tests is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported by each registrant.

If the registration of the substance by any registrant covers different grades, the sample used for the new tests must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.