EUROPEAN CHEMICALS AGENCY

Helsinki, 28 October 2019

Addressee: [redacted]

Decision number: CCH-D-2114484865-31-01/F
Substance name: Disodium wolframate
EC number: 236-743-4
CAS number: 13472-45-2
Registration number: [redacted]
Submission number: [redacted]
Submission date: 16/10/2018
Registered tonnage band: Over 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. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) in a first species (rat or rabbit), oral route with the registered substance;**

2. **Pre-natal developmental toxicity study (Annex X, Section 8.7.2.; test method: OECD TG 414) in a second species (rat or rabbit), oral route with the registered substance;**

You have to submit the requested information in an updated registration dossier by ***5 May 2021***. You shall also update the chemical safety report, where relevant. The deadline 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, 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 1: Reasons

1. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.) in a first species

In accordance with Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at more than 1000 tonnes per year must contain, as a minimum, the information specified in Annexes VII to X 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 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. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

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 XI, Section 1.1.2. In the technical dossier you have provided the following study record:

> Key study: "*Combined Repeated Dose Toxicity Study with the Reproduction /Developmental Toxicity Study*", rat, oral (equivalent or similar to EPA OPPTS 870.3650; GLP not specified) with the registered substance at 5, 62.5, and 125 mg/kg bw/day (EC no: 236-743-4), 70-days, McInturf et al.; 2008 and 2011 (publications).

However, ECHA notes that your adaptation does not meet general rule for adaptation of Annex XI; Section 1.1.2 because this study does not provide the information required by Annex IX, Section 8.7.2. since it does not cover key parameters of a pre-natal developmental toxicity study like examination of foetuses for skeletal and visceral alterations. In addition, the dose levels used in the study are considered not sufficient as no toxic effects were observed at the highest dose level which is much lower than the limit dose level. Hence, the results do not have an adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3) of the REACH Regulation, and data are not adequate for the purpose of classification and labelling and/or risk assessment. 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.

According to the test method OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default assumption ECHA considers testing should be performed with rats or rabbits as a first 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 solid, ECHA concludes that testing should be performed by the oral route.

In your comments on the draft decision, you firstly refer to the coverage of the key parameters of a pre-natal developmental toxicity study by the US EPA Guideline OPPTS 870.3650 (equivalent to OECD TG 422) – Combined Repeated Dose Toxicity Study with the Reproduction-Developmental Toxicity Study. ECHA underlines that a pre-natal developmental toxicity study according to OECD TG 414 includes examination of skeletal and visceral alterations of foetuses as key parameters. The US EPA Guideline OPPTS 870.3650 study requires that the pups should, at least, be carefully examined externally for gross abnormalities. In your comments you state that gross necropsy of the offspring also includes examination of visceral malformations. However, no skeletal alterations (malformation and variations) were examined. Thus, key parameters are still missing.

With respect to the dose levels, you indicate that a 250 mg/kg bw/day dose group was initially included in the study and that a significantly decreased body-weight gain in the P0 males and gestational weight gain was observed, as well as increasing gestational length (1.2 days) in the dams. Additionally, at this dose level the litter size and the average weight per pup decreased, while the effect was not significant. No clinical signs or effects on pup viability were observed. However, ECHA notes that the dose at 250 mg/kg bw/day, initially included in the study design, has not been included in the study record provided in the IUCLID dossier, and neither in the publications by McInturf, S. *et al.* (2008 and 2011). Therefore, ECHA cannot perform a scientific assessment of the relevant findings or assess whether this dose level can be considered to comply with OECD TG 414 in aiming to induce some developmental and/or maternal toxicity.

Moreover, you refer to the preliminary results of an on-going US NTP perinatal study in drinking water in Sprague-Dawley rats on the registered substance (EC 236-743-4) conducted according EPA Health Effects Test Guidelines OPPTS 870.3650 (which is similar to OECD TG 422) at doses of 0, 125, 250, 500, 1000, or 2000 mg/L. ECHA underlines that this study will not provide the information required by Annex IX, Section 8.7.2. since the EPA OPPTS 870.3650 TG guideline does not cover key parameters of a pre-natal developmental toxicity study like e.g. examination of foetuses for skeletal alterations. Hence, the results of such study will not have an adequate and reliable coverage of the key parameters addressed in the corresponding test method referred to in Article 13(3) of the REACH Regulation, and data will not be adequate for the purpose of classification and labelling and/or risk assessment.

Finally, you suggest performing an OECD TG 414 in rabbits as the first species, since it can be concluded from the McInturf study (McInturf *et al.* 2008; McInturf *et al.* 2011) that no effects of a prenatal treatment were observed in rats. ECHA underlines that pre-natal developmental toxicity studies (test method OECD TG 414) on two species are part of the standard information requirements of the REACH Regulation for a substance registered for 1000 tonnes or more per year. ECHA notes that the technical dossier does not contain information on any valid pre-natal developmental toxicity study as required according to Section 8.7.2. of Annex IX and X. As indicated in the request section of this decision (first page), it is at your discretion to decide which species to test in the first pre-natal developmental toxicity study.

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: OECD TG 414) in a first species (rat or rabbit) by the oral route.

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

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

Pre-natal developmental toxicity studies (test method OECD TG 414) on two species are part of the standard information requirements for a substance registered for 1000 tonnes or more per year (Annex IX, Section 8.7.2., column 1, Annex X, Section 8.7.2., column 1, and sentence 2 of introductory paragraph 2 of Annex X of the REACH Regulation).

ECHA notes that the technical dossier does not contain information on a pre-natal developmental toxicity study with the registered substance.

You have attempted to adapt this standard information requirement and provided in IUCLID section 7.8.2 the following justification for the adaptation: *"Based on the lack of developmental toxicity in rats, the need to conduct a second developmental study on a second species is not required".*

However, ECHA notes that a pre-natal developmental study on a second species is a standard information requirement and thus your adaptation does not meet the specific rules for adaptation of Annex X, Section 8.7.2., column 2 nor the general rules for adaptation of Annex XI.

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.

According to the test method OECD TG 414, the rat is the preferred rodent species and the rabbit the preferred non-rodent species. On the basis of this default consideration, ECHA considers testing should be performed with rabbits or rats as a second species, depending on the species tested in the first pre-natal developmental toxicity study.

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 solid, ECHA concludes that testing should be performed by the oral route.

In your comments on the draft decision, you state that the rat oral reproductive/developmental toxicity study (McInturf *et al.* 2008; McInturf *et al.* 2011) on the registered substance showed absence of physical birth defects, including missing digits in pups, and the preliminary results of the US NTP perinatal study conducted according to EPA OPPTS 870.3650 (equivalent to OECD TG 422) in rats shows a lack of birth defects. On these basis, you propose to wait for the result of the ongoing NTP rat perinatal study on the registered substance before taking a decision to conduct an OECD TG 414 oral study in rabbits with the registered susbtance.

However, ECHA underlines that a pre-natal developmental study according to OECD TG 414 on a second species is a standard information requirement under REACH (Annex X, Section 8.7.2). A study according to EPA OPPTS 870.3650 will not provide the information required at Annex IX and X, Section 8.7.2, since the EPA OPPTS 870.3650 TG guideline does not cover key parameters of a pre-natal developmental toxicity study like e.g. examination of foetuses for skeletal alterations as explained above.

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: OECD TG 414) in a second species (rabbit or rat) by the oral route.

Notes for your consideration

You are reminded that before performing a pre-natal developmental toxicity study in a second species you must consider the specific adaptation possibilities of Annex X, Section 8.7., column 2 and general adaptation possibilities of Annex XI. If the results of the test in the first species with other available information enable such adaptation, testing in the second species should be omitted and the registration dossier should be updated containing the corresponding adaptation statement.

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 25 October 2018.

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 within 30 days of the notification.

ECHA took into account your comments and did not amend the requests.

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 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 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.