EUROPEAN CHEMICALS AGENCY

Helsinki, 28 October 2019

Addressee: [redacted]

Decision number: CCH-D-2114484606-39-01/F
Substance name: Dihydrogen wolframate
EC number: 231-975-2
CAS number: 7783-03-1
Registration number: [redacted]
Submission number: [redacted]
Submission date: 15/10/2018
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. **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 either with the analogue substance sodium tungstate (EC no 236-743-4) or with the registered substance;**

You have to submit the requested information in an updated registration dossier by ***4 November 2020***. You shall also update the chemical safety report, where relevant.

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.

You have sought to adapt this information requirement according to Annex XI, Section 1.5. of the REACH Regulation by providing the following information:

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 read-across substance sodium tungstate at 5, 62.5, and 125 mg/kg bw/day (EC no: 236-743-4), 70-days, [redacted] 2007 (study report), 2008 and 2011 (publications). In the study record in section 7.8.2 of the IUCLID dossier you further explained: "*No fertility, reproductive, or developmental toxicity data of sufficient quality are available for tungstic acid (target substance). However, developmental toxicity data are available for sodium tungstate (source substance), which will be used for reading across.*"

Read across Approach

ECHA has assessed the read-across approach applied to fulfil the standard information requirement of a "pre-natal developmental toxicity study" at Annex IX, Section 8.7.2. of the REACH Regulation.

ECHA notes that Annex XI, Section 1.5. requires a structural similarity among the substances within a group or category such that relevant properties of a substance within the group can be predicted from the data on reference substance(s) within the group by interpolation. The similarities may be based on: (1) a common functional group; (2) the common precursors and/or the likelihood of common breakdown products via physical and biological processes, which result in structurally similar chemicals; or (3) a constant pattern in the changing of the potency of the properties among the substances. The following analysis presents your justification for the proposed grouping approach and read-across hypothesis, together with ECHA's analysis concerning the justification in both a generic and an endpoint-specific context.

Description of the read-across approach proposed by you

ECHA notes that in section 7.8.2 of the IUCLID dossier you have indicated the use of data from a source substance sodium tungstate (EC no 236-743-4) to fill the data gap for the pre-natal developmental toxicity requirement in a first species for the target substance (tungstic acid) which explains that: "*Due to lower water solubility and lower toxicity for the target substance compared to the source substance, the resulting read across from the source substance to the target substance is appropriate as a conservative estimate of*

potential toxicity for this endpoint. In addition, read across is appropriate because the classification and labelling is more protective for the source substance than the target substance, the PBT/vPvB profile is the same, and the dose descriptors are, or are expected to be, lower for the source substance".

Additionally, you have provided a read-across justification as a separate document in Annex I of the Chemical Safety Report (CSR) named "[redacted]". The read-across category approach includes 10 tungsten substances registered under REACH.

In the read-across justification document you provide the following hypothesis: *"The tungsten substances read-across approach category hypothesis is based on the rate and extent to which tungsten substances can produce soluble available ionic species, in this case tungstate (WO_4^{2-}). Therefore, the hypothesis for tungsten substances read-across category approach rely on the WO_4^{2-} ion being bioavailable than on a strict interpretation of structural similarity".* You concluded that *"the hypothesis is based on transformation to a common compound".*

You claim that the read-across approach is justified by weight of evidence based on the studies you provided on:

- Transformation/dissolution (T/D)
- *In vitro* bioaccessibility (bioelution)
- *In vivo* toxicokinetics

In addition, you provided the following assumptions underlying the grouping of tungsten substances for estimating their toxicological properties:

- The metal ion tungstate is responsible for the effects to be assessed (the toxicity of the counter ion is assumed to be largely irrelevant in producing the effects to be assessed);
- The water solubility basis of grouping the tungsten substances has been assessed by transformation/dissolution and bioaccessibility/bioelution studies;
- The metal ion is mainly responsible for the systemic effects. This was not, however, confirmed for local mammalian toxic effects as acute dermal, skin and eye irritation and sensitization studies were conducted on the target substances. Therefore, the assumption may not be applicable for local mammalian toxic effects;
- Differences in the toxicity due to different oxidation states of the metal ion are considered not relevant since all the tungsten substances will produce soluble available ion in the same oxidation state (+6); i.e. tungstate ion (WO_4^{2-}).

ECHA analysis of the read-across approach for pre-natal developmental toxicity properties

In order to meet the provisions in Annex XI 1.5 to predict physicochemical and toxicological properties from data for a reference substance within the group by interpolation to other substances in the group, ECHA considers that structural similarity alone is not sufficient. It has to be justified why such prediction is possible in view of the identified structural differences and the provided evidence has to support such explanation. In particular, the structural similarities must be linked to a scientific explanation of how and why a prediction is possible.

ECHA has assessed the read-across approach based on the hypothesis of the transformation in solution (speciation) to a common compound (tungstate) for the target and source

substances. ECHA notes that water solubility of these substances is an important factor in determining their bioavailability. In addition, ECHA has assessed whether the proposed read-across from sodium tungstate to the target substance represents an appropriate worst-case for pre-natal developmental toxicity properties. ECHA has addressed each line of evidence as follows.

Transformation/Dissolution studies on tungsten substances

ECHA understands that you intend to use a read-across approach where structurally similar substances have a common breakdown product via physical and biological processes. You claim that the hypothesis for the tungsten substances read-across approach relies on the WO_4^{2-} ion being bioavailable.

You also state that (1) the toxicity of the counter ion is assumed to be largely irrelevant in producing the effects to be assessed and (2) differences in the toxicity due to different oxidation states of the metal ion are considered not relevant.

In terms of data, in your read-across justification document you reported the results of transformation/dissolution studies which provide the total dissolved tungsten concentration measured for several tungsten substances (sodium tungstate, ammonium paratungstate, ammonium metatungstate, tungsten metal, tungsten trioxide, tungsten dioxide, tungsten oxide, tungsten carbide and tungsten disulphide) using ICP-MS while the speciation of soluble tungsten fraction (WO_4^{2-}) was measured using HPLC. The results show that the WO_4^{2-} anion was the predominant tungsten-bearing species in solution for all tungsten substances examined at pH 6 and 8.5.

Based on these data, ECHA concludes that the tungstate ion is the predominant form of soluble tungsten in solution at pH 6 and 8.5. The results also show that for the tungsten substances tested there were differences in the levels of soluble tungsten and that sodium tungstate releases a comparatively higher level of soluble tungsten compared to the sparingly water soluble tungsten substances.

ECHA also agrees that the toxicity of the counter ions (e.g. Na^+, H^+) is considered to be largely irrelevant in producing the effects to be assessed.

ECHA agrees that speciation, i.e. the occurrence of metal in different forms, is often a critical parameter in the toxicity of metals affecting e.g. the bioavailability of metals and toxicity at the cellular level.

Bioaccessibility/Bioelution studies in biological fluids

In the read-across justification document, you state that "*For metal substances, it is the bioavailability, defined as the degree of the metal ion (or a redox form of this ion) that enters systemic circulation and thereby accessing target sites, that determines the potential adverse effects.*" You further explain that "*Bioaccessibility is measured as the in vitro dissolution in synthetic biological fluids, which is a surrogate for the amount of a substance (eg metal ion) available for absorption, eg for bioavailability. Bioelution can be used as a tool to measure bioaccessibility and provide an estimate of bioavailability.*"

ECHA agrees that the bioaccessibility is a surrogate comparative measure for the amount of a metal ion that is potentially available for absorption. Additionally it is the bioavailability of metal substances, i.e. the degree of the metal ion that enters the systemic circulation

accessing the target sites, that determines the potential for systemically-mediated adverse effects.

In terms of data, you have included the results of a series of bioelution studies on six sparingly soluble tungsten substances (tungsten oxide, tungsten trioxide, tungsten dioxide, tungsten metal, tungsten carbide, reaction mass of ditungsten carbide and tungsten carbide, tungsten disulphide) in five biological surrogate biofluids representing the three major exposure routes: oral (gastric fluid), inhalation (alveolar, interstitial, and lysosomal fluids) and dermal (perspiration/sweat fluid). You explained that the aim is to present an estimation of the bioavailable fraction of tungstate which may be released from each of the tungstate substances under physiological conditions. The study design excluded sodium tungstate since the substance is widely absorbed, distributed and excreted as demonstrated in toxicokinetic studies (see next paragraph). You also explained that the objective of the bioelution study is comparative, i.e. the target substance is compared to sodium tungstate (the source substance).

ECHA notes that at pH 1.5 in simulated gastric fluid which represents the oral route, the default route of exposure in pre-natal developmental toxicity studies, all tested sparingly water-soluble tungsten substances including the target substance had low bioaccessibility (less than 1 %) based on the bioelution studies.

An important aspect is confirmation of bioaccessibility. ECHA notes that you have bioelution data on the target substance but not on the source substance. ECHA also notes, however, that you have submitted toxicokinetic data on the water-soluble sodium tungstate (the source substance) that allow for confirmation of bioaccessibility (see below).

Toxicokinetics (TK) studies

One important aspect in establishing that substances have similar effects or follow a regular pattern is the comparison of absorption, distribution, metabolism and elimination of source and target substances. This allows assessing the qualitative and quantitative internal systemic exposure of the test organism when exposed to source and target substances.

In terms of data, you presented several toxicokinetics studies conducted via oral or inhalation routes; one inhalation study in rats was on tungsten oxide and the rest of the studies were on sodium tungstate via oral or inhalation route in rats or mice. The purpose of presenting *in vivo* toxicokinetic data was to provide a biological verification and support of the bioelution data presented above. You explained that "*simple extraction methods may not accurately predict the bioavailability of substances in all cases, because biological processes can be complex*". With respect to the behaviour of the tungstate ion you reported that "*in vitro study has shown that WO_4^{2-} binds human albumin and other unknown protein; this finding was confirmed in rats, where approximately 80% of serum tungsten was bound to proteins, and most of the protein-bound tungsten was due to a complex with albumin*".

Based on the available *in vivo* toxicokinetic data, you conclude that sodium tungstate is readily absorbed, rapidly distributed to various organs (e.g. intestine, kidney, and femur) and excreted via the urine.

ECHA notes that you have provided *in vivo* toxicokinetics data on two tungsten substances, i.e. sodium tungstate (the source substance) and tungsten oxide. You have reported a number of studies have been conducted with single (gavage) or repeated oral dosing (drinking water) in rats or mice ([redacted] (2007), [redacted], (2008), [redacted]

[redacted] (2011) and [redacted] (2013)). The data show that water soluble tungstate (administered as sodium tungstate) is readily absorbed, measured in the plasma and distributed to a range of organs and tissues (including for example intestine, liver, kidney, and femur) and excreted via the urinary tract). Detectable tungsten was observed in the uterus and fetus in rats and mice administered sodium tungstate via drinking water for 14 days ([redacted], 2008). One of the studies ([redacted], 2013) reported that there was deposition and accumulation of tungsten in the bone of mice following administration of sodium tungstate in drinking water (estimated doses up to 250 mg/kg bw/day for up to 16 weeks).

As you have indicated, the purpose of *in vivo* toxicokinetic data is to provide biological verification and support of the bioelution data.

ECHA also notes that the water-soluble tungsten substances show similar or greater toxicity in acute oral toxicity studies compared with the sparingly water-soluble substances. However, toxicological similarity in one or multiple endpoints does not necessarily lead to predictable or similar human health properties in other endpoints.

ECHA concludes that the toxicokinetic information shows that following oral exposure water soluble sodium tungstate is readily absorbed, distributed and excreted therefore demonstrating that it is bioavailable.

Conclusion on the read-across approach for pre-natal developmental toxicity properties

ECHA concludes that the read-across approach for this endpoint is plausible taking together the toxicokinetic information (absorption, distribution, metabolism, elimination), the information on solubility, transformation/dissolution and on bioelution (bioavailability) as presented above. Therefore, ECHA concludes that the provided information supports the general hypothesis that sodium tungstate as a source substance will be a conservative approach to assess the pre-natal developmental toxicity of the target substance.

Nevertheless, although the proposed read-across approach is supported by adequate and reliable information, your adaptation of the information requirement is rejected due to lack of an adequate study, as described below.

Analysis of the study provided to fulfil the information requirements of Annex IX, Section 8.7.2

ECHA notes that you provided a "*Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test*" (equivalent or similar to EPA OPPTS 870.3650; GLP not specified) with the read-across substance sodium tungstate to fulfil the standard information requirement of Annex IX, Section 8.7.2. of the REACH Regulation.

However, ECHA notes that 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.

Study requested

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.

ECHA considers that the test shall be performed either with the analogue substance sodium tungstate (EC no 236-743-4), since the read-across is plausible, or with the registered substance subject to the present decision.

Similar requests are made in separate ECHA decisions on tungsten compounds to test either the registered substance or the analogue substance sodium tungstate for the same standard information requirements. You are recommended to consider testing the analogue substance since it could result in less vertebrate animals being tested rather than if each registered substance were tested.

If the test is conducted with the analogue substance, the eventual validity of the read-across approach will be reassessed after the submission of the information requested in this decision.

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 includes also 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 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, 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 sodium tungstate (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 [redacted] study ([redacted] 2008; [redacted] 2011) that no effects of a prenatal treatment were observed in rats. ECHA underlines that a pre-natal developmental toxicity study (test method OECD TG 414) on a first species is part of the standard information requirements of the REACH Regulation for a substance registered at 100 - 1000 tonnes 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.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived either with the analogue substance sodium tungstate (EC no 236-743-4) or with the registered substance subject to the presence decision: Pre-natal developmental toxicity study (test method: OECD TG 414) in a first species (rat or rabbit) by the oral route.

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.

4. If the required tests are conducted with an analogue substance in the context of a read-across approach, the identity of the test material used to perform the test should be specified in line with ECHA's Practical Guide on "How to use alternatives to animal testing to fulfil your information requirements" (chapter 4.4). This is required to show that the test material is representative of the analogue substance identified in the read-across approach and used to predict the properties of the registered substance.