Helsinki, 28 October 2019

Addressee: [redacted]

Decision number: CCH-D-2114484604-43-01/F
Substance name: Reaction mass of ditungsten carbide and tungsten carbide
List number: 915-093-1
CAS number: NS
Registration number: [redacted]
Submission number: [redacted]
Submission date: 23/10/2015
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, and 125 mg/kg bw/day (EC no: 236-743-4), 70-days, McInturf et al.; 2008 (publication).

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 according to Annex XI, Section 1.5., two conditions shall be necessarily fulfilled. Firstly, there needs to be structural similarity between source and target substances which results in a likelihood that these substances have similar physicochemical, toxicological and ecotoxicological properties. Secondly, it is required that the relevant properties of a target substance may be predicted from data for source substance (read-across approach). ECHA considers that the generation of information by such alternative means should offer equivalence to the information generated by prescribed tests or test methods.

Based on the above, a read-across hypothesis needs to be provided. This hypothesis establishes why a prediction for a toxicological or ecotoxicological property is reliable and should be based on recognition of the structural similarities and differences between the source and registered substances. This hypothesis explains why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern. The read-across approach must be justified scientifically and documented thoroughly, also taking into account the differences in the chemical structures. There may be several lines of supporting evidence used to justify the read-across hypothesis, with the aim of strengthening the case.

Due to the different nature of each endpoint and consequent difference in scientific considerations (e.g. key parameters, biological targets), a read-across must be specific to the endpoint or property under consideration. Key physicochemical properties may determine the fate of a compound, its partitioning into a specific phase or compartment and

largely influence the availability of compounds to organisms, e.g. in bioaccumulation and toxicity tests. Similarly, biotic and abiotic degradation may alter the fate and bioavailability of compounds as well as be themselves hazardous, bioaccumulative and/or persistent. Thus, physicochemical and degradation properties influence the human health and environmental properties of a substance and should be considered in read-across assessments. However, the information on physicochemical and degradation properties is only a part of the read-across hypothesis, and it is necessary to provide additional justification which is specific to the endpoint or property under consideration.

The ECHA Read-across assessment framework foresees that there are two options which may form the basis of the read-across hypothesis- (1) (Bio)transformation to common compound(s)- the read-across hypothesis is that different substances give rise to (the same) common compounds to which the organism is exposed and (2) Different compounds have the same type of effect(s)- the read-across hypothesis is that the organism is exposed to different compounds which have similar (eco)toxicological and fate properties as a result of structural similarity (and not as a result of exposure to common compounds).

Finally, Annex XI, Section 1.5. lists several additional requirements, which deal with the quality of the studies which are to be read-across.

Description of the grouping and read-across analogue approach proposed by you

In section 7.8.2 of the IUCLID dossier you have indicated the use of read-across from a structural analogue to fill the data gap for the requirement of a pre-natal developmental toxicity study in a first specie. Additionally you further explained : "*Due to a higher water solubility and dissolution rate of sodium tungstate dihydrate (source substance) than for fused carbide (target substance), the resulting toxicity potential would also be expected to higher for sodium tungstate, so read-across is conservative and appropriate. In addition, read-across is justified because the classification and labelling for the source substance is more protective than for the target substance and the PBT/vPvB profile is the same. Finally, the dose descriptors are, or are expected to be, higher for the target substance, and read-across to the source substance is protective.*".

Additionally, you have provided a read-across approach justification document in Annex I of the Chemical Safety Report (CSR) named "[redacted]".

In the read-across analogue approach justification document you provide the following hypothesis: "*For human health endpoints, it is the relative bioavailability of tungstate at target site(s) that in most cases determines the potential occurrence and the severity of the systemic effects to be assessed for the read-across of tungsten substances. Therefore, tungsten substances of similar release of the tungsten ionic species (i.e. similar solubility) at the exposure site are expected to result in similar systemic and local toxicity. In the absence of data for substances of similar tungsten ionic release, the approach in the read-across strategy is to assume that the specific tungsten-containing compound to be evaluated (i.e. the target substance) shows the same systemic hazards as more soluble tungsten substances, with the most protective tungsten compound for read-across being sodium tungstate as one of the most water-soluble tungsten-containing substances*".

Additionally you have provided the following justification "*The read-across strategy is predicated on the assumed presence and bioavailability of a common metal ion (WO_4^{2-}) in biological fluids after exposure to tungsten compounds.*"

In your justification you also indicated that the similarity between compounds for purposes of developing a read-across strategy is based on:

- Water solubility
- Transformation/Dissolution studies on tungsten substances
- Bioaccessibility/Bioelution studies in biological fluids
- Toxicity of tungsten substances

ECHA analysis of the grouping and 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 source substance to the target substance, 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 presence of a common tungsten constituent as a functional group and of transformation (speciation) to a common compound (tungstate ion) for the target and source substances. In addition, ECHA has assessed whether the proposed read-across from sodium tungstate (EC no 236-743-4) to the target substance represents an appropriate worst-case for prenatal developmental toxicity properties.

Water Solubility

In your read-across approach justification document you state that substances of similar water solubility would have similar toxicity and also that the extent of water solubility approximates the bioavailability of a substance. On these basis you conclude that: "*tungsten carbide and reaction mass of ditungsten carbide and tungsten carbide are sparingly water soluble (when measured in the bioaccesibility protocol), so read-across between the two substance is supported. Sodium tungstate has high water solubility and is a maximal estimate of tungsten release, so read-across from sodium tungstate to reaction mass of ditungsten carbide and tungsten carbide is an appropriate conservative read-across approach for reaction mass of ditungsten carbide and tungsten carbide for systemic effects*".

Your proposed adaptation argument is that a physico-chemical comparison between the source and registered substance is an important element in the prediction the properties of the registered substance and that the source substance, due to its much higher water solubility, results in a much higher release of tungstate ions and therefore can be used for predicting the properties of the registered substance. ECHA agrees that the comparison of the water solubility is an important aspect in determining the similarity and dissimilarities between compounds for the purposes of the read-across approach. ECHA notes that the bioelution data shows that the target substance has low solubility. However, a comparison of the physico-chemical properties does not necessarily lead to predictable human health properties. Thus a physico-chemical comparison per se, and more specifically a comparison of the water solubility, is not sufficient alone to enable the prediction of human health properties of a substance, and more specifically of pre-natal developmental toxicity properties. Other elements need to be considered in addition to water solubility (e.g. speciation and bioaccessibility) to estimate the bioavailable fraction of tungstate which may be released under physiological conditions.

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 products 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. The aim of the transformation/dissolution studies is to evaluate the rate and amount of tungsten ion released by the source and target substance and determine if WO_4^{2-} is the dominant soluble form of tungsten released from water-soluble and water-insoluble tungsten substances in aqueous media under the experimental conditions used.

In terms of data, in your read-across justification document you reported 24 hr transformation/dissolution studies at pH 8.5 for tungsten carbide and for the source substance (data at pH 6 were not shown). No measurement was reported on the target substance. You also indicated that the transformation/dissolution behaviour of reaction mass of ditungsten carbide and tungsten carbide is expected to be similar to that of tungsten carbide, due to the similarity in physico-chemical properties (both substances are sparingly soluble). The total dissolved tungsten concentration was measured 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 is the predominant tungsten-bearing species in solution for the tested tungsten substances examined at pH 8.5.

Based on this data, ECHA concludes that the tungstate ion is the predominant form of soluble tungsten in solution at pH 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 has a comparatively higher level of soluble tungsten compared to the sparingly water soluble tungsten substances (such as the target substance).

Bioaccessibility/Bioelution studies in biological fluids

In terms of data, in your read-across approach justification document you reported bioelution study results for the target substance in five different synthetic fluids representing different routes of human exposure: oral (gastric fluid), inhalation (alveolar, interstitial, and lysosomal fluids) and dermal (sweat fluid). You indicated that bioelution in synthetic biological fluids is one of the relevant parameters to be considered as an indicator of bioavailability. It represents a more useful parameter than water solubility or transformation/dissolution studies since it determines the solubility in solutions that are more relevant to physiological conditions. The aim is to illustrate the tungsten ion release for the target substance by different routes of exposure and to provide an estimate of the extent of bioavailability of the target 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, the target substance has very low bioavailability based on bioelution data. ECHA notes that the bioelution study design excluded sodium tungstate, however in the read-across data matrix of your read-across justification document under the bioaccessibility data you stated that the solubility of sodium tungstate in these fluids is significantly higher than the target substance. Additionally in the transformation/dissolution study, you indicate that sodium tungstate is clearly more water soluble compared to the target substance claiming that this suggests that also bioavailability would be markedly higher for sodium tungstate.

ECHA agrees that the target substance has very low bioavailability in the bioelution study. 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 that you have not submitted toxicokinetic data on the water-soluble sodium tungstate (the source substance) that allow for confirmation of bioaccessibility (see below).

Toxicity of tungsten substances

In your read-across justification document, you indicate that other supporting information can be used to support the read-across strategy, including similarity in toxicological data. In this respect, you include consideration on similarities in toxicological properties in certain short-term toxicity studies between tungsten carbide and the source substance (e.g. acute toxicity, skin sensitisation, and skin and eye irritation). You indicate that few long-term data are available which allow comparison of the toxicological profiles of the source and target substances, however, based on consideration on the bioelution results and on the composition, you indicated that tungsten carbide and sodium tungstate are expected to capture the range of toxicity of the target substance and on the basis that the sodium tungstate as a source substance represents a conservative approach.

ECHA notes that no human health effects data are available from studies conducted with the registered substance. The available data show that acute toxicity data, as well as skin and eye irritation and skin sensitisation data, indicate that the tungsten substances tested show broadly similar (low) toxicity with respect to the above mentioned endpoints. In addition you consider use of acute toxicity results from sodium tungstate or tungsten oxide to represent a conservative approach.

ECHA further notes that toxicological similarity in one or multiple endpoints does not necessarily lead to predictable or similar human health properties in other endpoints. Thus toxicological similarity on certain endpoints is not sufficient to enable the prediction of other human health properties of a substance and more specifically of the pre-natal developmental toxicity properties.

Such comparison of the information from studies with single dosing is of limited value to the assessment of the toxicokinetics of the substances under the conditions of repeated oral exposure which would be investigated in the requested study.

Toxicokinetics

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.

ECHA notes that there are existing *in vivo* toxicokinetic studies on the source substance(s) have been conducted and you have not provided them either in your technical dossiers or in your read-across justification document. Such studies have been reviewed in Lemus R and Venezia C, Crit Rev Toxicol 2015: 45(5) 388-411. These cited studies elucidate the toxicokinetic profiles of the source substances in rats and/or mice, though oral and inhalation administration and following single or repeated exposures. Such studies are necessary to consolidate the read across approach.

ECHA concludes that such information is an essential piece of information to support your hypothesis. In the absence of such information in the registration ECHA is not currently in a position to verify the biological validity of your read-across approach.

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

ECHA considers that although you have provided relevant data in the justification document to support the read-across approach, you have not fully established why a prediction for a specific human health property is reliable. Additionally, ECHA observes that you did not provide essential information in support of your hypothesis that sodium tungstate (the source substance) represents an appropriate worst-case for prenatal developmental toxicity properties. Such information may be provided through e.g. toxicokinetic studies. In the absence of supporting information showing that the sodium tungstate is absorbed, distributed to the various organs and excreted, there is not an adequate basis for predicting the properties of the registered substance from the data obtained with the source substance with respect to the pre-natal developmental toxicity properties.

ECHA notes that you provided comments and included therein a read-across justification document named "[redacted]", which you indicate is also included in a dossier update.

This document contains *in vivo* toxicokinetic data demonstrating that sodium tungstate is readily absorbed, rapidly distributed to various organs (e.g. intestine, kidney, and femur) and excreted via the urine. This supports the hypothesis that sodium tungstate represents an appropriate worst-case scenario for pre-natal developmental toxicity properties of the registered substance.

Based on the updated read-across justification document and your comments, ECHA concludes that the read-across for the pre-natal developmental toxicity study is supported by adequate and reliable information.

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.

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 present 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

ECHA notes that the tonnage band for several members of the joint submission is 100 to 1000 tonnes per year.

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 amended 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.