~~Confidential~~

Helsinki, 20 October 2020

Addressees
Registrant of JS_701-326-2 as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
23/03/2020

Registered substance subject to this decision ("the Substance")
Substance name: reaction mass of (3ar,5as,9as,9br)-3a,6,6,9a-tetramethyldodecahydronaphtho[2,1-b]furan and (3as,5ar,9ar,9bs)-3a,6,6,9a-tetramethyldodecahydronaphtho[2,1-b]furan
EC number: 701-326-2
CAS number: NS

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

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by the deadline of ***27 April 2022***.

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

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

1. Sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.; test method: OECD TG 408) by oral route, in rats, modified to include urinalysis and immuno-histochemical investigation of renal pathology allowing the determination of whether the pathology is mediated by alpha-2u globulin nephropathy

2. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: OECD TG 414) by oral route, in one species (rat or rabbit)

Reasons for the request(s) are explained in the Appendix entitled "Reasons to request information required under Annex IX of REACH".

Information required depends on your tonnage band

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

- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 tpa

How to comply with your information requirements

To comply with your information requirements you must submit the information requested by this decision in an updated registration dossier by the deadline indicated above. You must

also update the chemical safety report, where relevant, including any changes to classification and labelling, based on the newly generated information.

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

Appeal

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

Failure to comply

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

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

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

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

1. Sub-chronic toxicity study (90-day)

A Sub-chronic toxicity study (90 day) is a standard information requirement under Annex IX to REACH.

Although you do not explicitly claim an adaptation according to Column 2 of Annex IX, Section 8.6.2., ECHA understands that you have sought to adapt this information requirement based on the following arguments in your dossier:

- *"ST 10 C 08 has a relatively low molecular weight of 236.4 g/mol. The substance is slightly soluble in water (1.88 mg/L), highly lipophilic (log Pow = 5.09), not volatile (vapour pressure = 0.054 Pa at 20°C) and not inhalable (particle size > 100 µm)."*
- *"Although the physical chemical properties suggest that ST 10 C 08 is of adequate molecular size to participate in endogenous absorption mechanisms within the mammalian gastrointestinal tract, the acute oral and the combined repeated dose toxicity with the reproduction/developmental screening test identified neither significant evidence of toxicity nor indication of reproductive and developmental toxicity (LD50 > 2000 mg/kg bw and NOAEL systemic toxicity, fertility and development = 800 mg/kg bw/day, respectively)."*
- *"ST 10 C 08 was not tested for acute toxicity following dermal application, but a study is available on one of its enantiomers (LD50 > 2000 mg/kg bw/day). The single-dose dermal application of the substance did not result in any systemic toxicity that would suggest systemic absorption through cutaneous barriers. Moreover, enhanced skin penetration is not expected as ST 10 C 08 is not a skin irritant or corrosive."*
- *"The potential for inhalation toxicity was not evaluated in vivo. However, the vapour pressure and the granulometry of ST 10 C 08 indicated an absence of volatility and inhalability; therefore no exposure by inhalation is anticipated. Thus, at ambient temperature, no respiratory absorption is expected under normal use and handling of the substance."*

We have assessed this information and identified the following issue:

As provided in Annex IX, Section 8.6.2, Column 2, you may adapt the information requirement, provided you fulfil the following criterion:

- the Substance is unreactive, insoluble and not inhalable and there is no evidence of absorption and of toxicity in a 28-day 'limit test', particularly if it is coupled with limited human exposure.

You state as a conclusion that the Substance *"is of low reactivity, only slightly soluble, and not inhalable at ambient temperature and there was no evidence of toxicity in the combined study in which animals were exposed 4 to 6 weeks. Therefore, although absorption potential is expected, it is not deemed necessary to perform a 90-day study."*

You have not demonstrated that the Substance is unreactive and insoluble, that there is no evidence of absorption and toxicity and that there is limited human exposure. On the contrary, you state that the Substance is of *"low reactivity, only slightly soluble"*, which would indicate that the column 2 requirements are not fulfilled. You also conclude that absorption potential is expected. This is supported by the systemic effects observed in a screening study (e.g. centrilobular hepatocellular hypertrophy in the liver and tubular basophilia in the kidneys). Additionally, you conclude in your dossier that *"the observation of systemic effects, even if of very low toxicological concern, indicates the oral bioavailability of the substance and/or its metabolites*. Finally, the identified uses (e.g. widespread uses by professionals, and consumer

uses) indicate that there is potential for significant human exposure. Therefore, your adaptation is rejected.

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

Information on the design of the study to be performed

Referring to the criteria provided in Annex IX, Section 8.6.2, Column 2, the oral route is the most appropriate route of administration to investigate repeated dose toxicity, because the Substance is a solid and it is reported that 99.9% of the particles are > 100 µm and there are no particles of inhalable size (< 50 µm).

The screening study (OECD TG 422) you submitted showed that adverse effects such as increased degrees of severity of hyaline inclusions along with an increased incidence and severity of tubular basophilia at medium and high dose, i.e. at 400 and 800 mg/kg bw/d, were observed in the kidneys of male rats but not in male control rats or in any exposed/control female rats.

This indicates that the kidney is a target organ of the Substance which may induce alpha-2u-globulin-mediated nephropathy. Since this mode of action is considered not relevant to humans, the involvement of alpha-2u-globulin in the kidney effects is a key parameter for establishing the relevance of the kidney effects for risk assessment. You consider that hyaline inclusions represent alpha-2-microglobulin but do not provide any direct evidence to support this conclusion.

Therefore, although optional (as per paragraph 37 of OECD TG 408), a urinalysis is required to investigate further the kidney function after administration of the Substance. Additionally, a full histopathological examination (paragraphs 45 and 47 of OECD TG 408), including immune-histochemical investigation of renal pathology is required to determine if the pathology is mediated by alpha-2u globulin.

2. Pre-natal developmental toxicity study in one species

A Pre-natal developmental toxicity (PNDT) study (OECD TG 414) in one species is a standard information requirement under Annex IX to REACH.

Although you do not explicitly claim an adaptation according to Column 2 of Annex IX, Section 8.7., ECHA understands that you have sought to adapt this information requirement based on the following arguments in your dossier:

- *"ST 10 C 08 has a relatively low molecular weight of 236.4 g/mol. The substance is slightly soluble in water (1.88 mg/L), highly lipophilic (log Pow = 5.09), not volatile (vapour pressure = 0.054 Pa at 20°C) and not inhalable (particle size > 100 µm)."*
- *"Although the physical chemical properties suggest that ST 10 C 08 is of adequate molecular size to participate in endogenous absorption mechanisms within the mammalian gastrointestinal tract, the acute oral and the combined repeated dose toxicity with the reproduction/developmental screening test identified neither significant evidence of toxicity nor indication of reproductive and developmental toxicity (LD50 > 2000 mg/kg bw and NOAEL systemic toxicity, fertility and development = 800 mg/kg bw/day, respectively)."*
- *"ST 10 C 08 was not tested for acute toxicity following dermal application, but a study is available on one of its enantiomers (LD50 > 2000 mg/kg bw/day). The single-dose dermal application of the substance did not result in any systemic toxicity that would suggest systemic absorption through cutaneous barriers. Moreover, enhanced skin*

penetration is not expected as ST 10 C 08 is not a skin irritant or corrosive."

- *"The potential for inhalation toxicity was not evaluated in vivo. However, the vapour pressure and the granulometry of ST 10 C 08 indicated an absence of volatility and inhalability; therefore no exposure by inhalation is anticipated. Thus, at ambient temperature, no respiratory absorption is expected under normal use and handling of the substance."*
- *"Therefore, further studies to investigate developmental toxicity are considered to be scientifically unjustified."*

According to Annex IX, Section 8.7., Column 2, third indent, the study does not need to be conducted if the substance is of low toxicological activity. This needs to be demonstrated by meeting the following criteria:

- there is no evidence of toxicity seen in any of the tests available; and
- it can be proven from toxicokinetic data that no systemic absorption occurs via relevant routes of exposure; and
- there is no or no significant human exposure.

In your adaptation, you have not proven that there is no evidence of toxicity seen in any of the tests available. The provided screening study (OECD TG 422) with the Substance via oral route in rats indicates systemic effects including centrilobular hepatocellular hypertrophy in the liver and tubular basophilia in the kidneys. In addition, you have not provided any toxicokinetic data to show that there is no systemic absorption. On the contrary, you conclude in your dossier that *"the observation of systemic effects, even if of very low toxicological concern, indicates the oral bioavailability of the substance and/or its metabolites*. Finally, the uses of the Substance (e.g. widespread uses by professionals, and consumer uses) indicate that there is potential for significant human exposure.

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

A PNDT study according to the test method OECD TG 414 must be performed in rat or rabbit as preferred species with oral[2] administration of the Substance.

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

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

A. Test methods, GLP requirements and reporting

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

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

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

B. Test material

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

1. Selection of the Test material(s)

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

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

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

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[4].

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

Appendix C: Procedure

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

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

The compliance check was initiated on 20 November 2019.

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

ECHA did not receive any comments within the notification period.

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

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

Appendix D: List of references - ECHA Guidance[5] and other supporting documents

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

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

Read-across assessment framework (RAAF, March 2017)[6]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[6]

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

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

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

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

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

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

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

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

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

OECD Guidance documents[7]

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

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

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

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

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

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

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

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

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