Helsinki, 14 May 2020

Addressees
Registrant(s) of JS_TSH_[redacted] as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
28 March 2018

Registered substance subject to this decision ("the Substance")
Substance name: Toluene-4-sulphonohydrazide
EC number: 216-407-3
CAS number: 1576-35-8

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

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 ***21 February 2022***.

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

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

1. Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.; test method: EU C.2./OECD TG 202)

2. Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.; test method: EU C.3./OECD TG 201)

B. Information required from all the Registrants subject to Annex VIII of REACH

1. Transgenic rodent somatic and germ cell gene mutation assays (Annex VIII, Section 8.4., column 2; test method: EU B.58/OECD TG 488) in transgenic mice or rats, oral route on the following tissues: liver and glandular stomach; duodenum must be harvested and stored for up to 5 years. Duodenum must be analysed if the results of the glandular stomach and of the liver are negative or inconclusive.

   OR

   In vivo mammalian alkaline comet assay (Annex VIII, Section 8.4., column 2; test method: OECD TG 489) in rats, oral route, on the following tissues: liver, glandular stomach and duodenum.

2. Short-term repeated dose toxicity (28 days; Annex VIII, Section 8.6.1.) to be combined with the Screening for reproductive/developmental toxicity, as requested in B.3.

3. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test

method: EU B.64/OECD TG 422) by oral route, in rats

4. Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.; test method: OECD TG 203)

Reasons for the request(s) are explained in the following appendices:

- Appendix entitled "Reasons common to several requests";
- Appendices entitled "Reasons to request information required under Annexes VII to VIII of REACH", respectively.

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 and VIII to REACH, for registration at 10-100 tpa.

You are only required to share the costs of information that you must submit to fulfil your information requirements.

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.

Approved[1] under the authority of Christel Schillinger-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 on Reasons common to several requests

1. Assessment of your read-across approach under Annex XI, Section 1.5.

You propose to provide information on the following standard information requirements of the Substance by using grouping and read-across approach under Annex XI, Section 1.5:

- In vivo mammalian erythrocyte micronucleus test (Annex IX, Section 8.4., column 2)
- Short-term repeated dose toxicity (28 day), (Annex VIII, Section 8.6.1.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Short-term toxicity testing on aquatic invertebrates (Annex VII, Section 9.1.1.)
- Growth inhibition study aquatic plants (Annex VII, Section 9.1.2.)
- Short-term toxicity testing on fish (Annex VIII, Section 9.1.3.)

ECHA has considered the scientific and regulatory validity of your read-across approach(es) in general before assessing the specific standard information requirements in the following appendices.

Annex XI, Section 1.5. specifies two conditions which must be fulfilled whenever a read-across approach is used. Firstly, there needs to be structural similarity between substances which results in a likelihood that the substances have similar physicochemical, toxicological and ecotoxicological properties so that the substances may be considered as a group or category. Secondly, it is required that the relevant properties of a substance within the group may be predicted from data for reference substance(s) within the group.
Additional information on what is necessary when justifying a read-across approach can be found in the ECHA Guidance[2] and related documents[3, 4].

A. Predictions for toxicological properties

You provide read-across justification documents in IUCLID Section 13.

You predict the properties of the Substance from information obtained with the source substance 4,4'-oxydi(benzenesulphonohydrazide) (OBSH); EC No. 201-286-1 (CAS No. 80-51-3).

You provide the following reasoning for the prediction of toxicological properties: *"Due to the close structural similarity the data from toxicity testing of the source substance OBSH [...] is considered to reflect the toxicity of p-TSH [...] as the source and the target substances can be considered as two structural very comparable organic arylsulphonylhydrazides."*

Based on the above, ECHA understands that you predict the properties of the Substance using a read-across hypothesis which assumes that different compounds have the same type of effects. You predict that the properties of your Substance are to be quantitatively equal to those of the source substance.

You have not established a reliable basis for predicting toxicological properties for the following reasons:

i. Read-across hypothesis

[2] ECHA Guidance R.6
[3] RAAF, March 2017
[4] RAAF UVCB, March 2017

A read-across hypothesis needs to be provided, establishing why a prediction for a toxicological or ecotoxicological property is reliable. This hypothesis should be based on recognition of the structural similarities and differences between the source substance(s) and your Substance[5]. It should explain why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern.

Your read-across hypothesis is that the similarity in chemical structure between the source substance(s) and the Substance is a sufficient basis for predicting the properties of the Substance for other endpoints.

Similarity in chemical structure does not necessarily lead to predictable or similar toxicological properties in other endpoints. Additionally, there are differences in the structures between the source substance and the Substance, and you have not considered the impact of these differences on the prediction.
Therefore, you have not provided a well-founded hypothesis to establish a reliable prediction for the toxicological properties based on recognition of the structural similarities and differences between the source substances and the Substance.

ii. Provided information contradicts the read-across hypothesis

Annex XI, Section 1.5. provides that "substances whose physicochemical, toxicological and eco-toxicological properties are likely to be similar or follow a regular pattern as result of structural similarity may be considered as a group or 'category' of substances. The ECHA Guidance[6] indicates that "*it is important to provide supporting information to strengthen the rationale for the read-across*". The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the Substance can be predicted from the data on the source substance(s). The observation of differences in the toxicological properties between the source substance(s) and the Substance is a warning sign. An explanation for such a difference resulting in a contradiction between the similarities in properties claimed in the read-across hypothesis and the observation of different properties needs to be provided and supported by scientific evidence.
As indicated above, your read-across hypothesis is based on the assumption that the structurally similar target and source substances cause the same type of effect(s).

In addition to the read-across hypothesis above, you state that "*In the assessment of p-TSH* [i.e. the Substance] *also data on hydrazine and toluene-4-sulphonic acid is included for read-across purposes as these substances may be generated by hydrolysis of p-TSH. Here especially the substance hydrazine may be considered of concern due to its toxic potential*"; and "*Furthermore, it should be noted that data on repeated dose toxicity by oral exposure indicate that the same target organs are affected by hydrazine and OBSH exposure, indicating that the hydrazine-content of OBSH and p-TSH may play a crucial role of the systemic toxicity of these substances*"; as well as "*The hydrolysis half-life for the source substance OBSH is considerable lower and thus the potential toxicity of liberated hydrazine is expected to more expressed for OBSH than for p-TSH*".

This statement contradicts your read-across hypothesis which states that the Substance and OBSH have the same effects and that the toxicity of the Substance is predicted to be the same as that of OBSH. With this statement you argue that OBSH should be the worst case compared to the Substance, based on hydrolysis (i.e. (bio)transformation to a common

[5] ECHA Guidance R.6
[6] ECHA Guidance R.6, Section R.6.2.2.1.f

product which drives toxicity). You support this with a statement that the Substance, OBSH and hydrazine have the same toxicological profile (i.e. the same target organs in repeated dose toxicity studies). In contast, ECHA notes that the non-common hydrolysis product of the Substance does not show any toxicity (p-toluene sulphonate has a NOAEL of 1000 mg/kg/day in an OECD TG 421 study according to its REACH registration). Therefore, the toxicity observed can only be explained by toxicity of the Substance itself or by toxicity of the common hydrolysis product hydrazine. Since the same toxicity profile is observed also for the Substance, OBSH and hydrazine, and is most severe for hydrazine, the most likely explanation is that the toxicity is caused by the common hydrolysis product, i.e. hydrazine. This is not however reflected in your hypothesis nor in your read-across approach.

The available information contradicts your read-across hypothesis whereby the structurally similar target and source substances cause the same type of effect(s).
Currently you have not demonstrated and justified that the properties of the source substance(s) and of the Substance are likely to be similar despite the observation of these differences.

iii. Missing supporting information

Annex XI, Section 1.5 of the REACH Regulation states that "*physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s)*". For this purpose "*it is important to provide supporting information to strengthen the rationale for the read-across*"[7]. The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the Substance can be predicted from the data on the source substance(s).

Supporting information must include toxicokinetic information which demonstrate the formation of the common compound and non-common compounds and/or bridging studies to compare the toxicity profile of the Substance and source substance(s) to confirm your claimed worst-case prediction.

Information regarding common compounds

As indicated above, ECHA considers that your read-across hypothesis should consider (bio)transformation of the Substance and of the source substance(s) to common compound(s). In this context, information characterising the rate and extent of the (bio)transformation of the Substance and of the source substance(s) is necessary to confirm the formation of the proposed common (bio)transformation product and to assess the impact of the exposure to the parent compounds.

You have not provided any toxicokinetic information. Instead, the abiotic hydrolysis rate which differs significantly between the source and the target substances is used to justify a worst-case prediction for toxicological properties.

However, hydrolysis under abiotic conditions is not the same as hydrolysis under physiological conditions following absorbtion. Both the source and target substances have abiotic hydrolysis half-lifes >6 hours, and even longer at low pH; thus hydrolysis is unlikely to occur before absorption. Therefore, abiotic hydrolysis is not a reliable prediction for rate of hydrolysis following absorption since both abiotic and enzymatic hydrolysis must be considered in your prediction of toxicological properties. Furthermore, as indicated above, the Substance, OBSH and hydrazine have the same toxicity profile which supports the notion that hydrolysis occurs

[7] ECHA Guidance R.6, Section R.6.2.2.1.f

in vivo. You have not provided any experimental data or other adequate and reliable information, neither about the (bio)transformation of your Substance nor about the (bio)transformation of the source substance.

In the absence of this information, you have not provided supporting evidence establishing the extent to which the common (bio)transformation product is formed. Therefore, you have not provided sufficient supporting information to strengthen the rationale for a worst case approach.

Information regarding non-common compounds

As indicated above, your read-across hypothesis is based on the (bio)transformation of the Substance and of the source substance(s) to a common compound(s). In this context, exposure to the Substance and of the source substance(s) may also lead to exposure to other compounds than the common compound of interest. The impact of exposure to these non-common compounds on the prediction of properties of the target needs to be assessed to ensure that a reliable prediction can be made.

You have not provided information on the non-common hydrolysis products.

ECHA understands that both source and target substances (i.e. the Substance) are structurally similar in that they are "benzenesulphonohydrazides" and as such they are likely to hydrolyse to form hydrazine (the common hydrolysis product) and uncommon hydrolysis products 4,4'-oxydi(benzenesulphonoate) and p-toluenesulphonate from the source and target substances, respectively. You have p-toluene sulphonic acid as source substance in your read-across justification. However, ECHA does not consider p-toluene sulphonic acid as an appropriate source substance, because it is p-toluenesulphonate that is formed following hydrolysis, not the acid. You have not provided any information on 4,4'-oxydi(benzenesulphonoate).

Therefore you have not provided sufficient supporting information to strengthen the rationale for the read-across.

iv. Classification as a result of the read-across approach

According to Annex XI, Section 1.5. whenever a grouping and read-across approach *'is applied, substances shall be classified and labelled on this basis'*.

In your read-across justification you list both OSBH and hydrazine as source substances. But you only apply the classification resulting from OSBH, e.g. Muta 2 and STOT RE2 (kidneys). With regard to hydrazine you acknowledge the harmonised classification which includes Carc Cat 1B. However, you argue that *"the level of concern for this endpoint is considered most appropriately addressed by the Muta 2 classification of p-TSH and thus, no further classification is warranted due to the lack of data."*

ECHA disagrees with this approach, because classification for one hazard class is not a valid reason not to classify for a different hazard class.

B. Predictions for ecotoxicological properties

You provide read-across justification documents in IUCLID Section 13.

You predict the properties of the Substance from information obtained with the source substance OBSH.

You provide the following reasoning for the prediction of aquatic toxicity properties: *"The hypothesis for a read-across approach from environmental toxicity data on OBSH is the similarity of the chemical structure and physical chemical properties of the two substances. Both the target substance and the source substance are based on benzylsulfonylhydrazide. (..) The main activity (toxicity) of both substances is assumed to be allocated to the hydrazide-groups, which will justify the read-across."*

In addition, you claim that: *"As the rate of hydrolysis of the target substance is lower than rate of hydrolysis of the source substance [and] the observed toxicity of OBSH is partly explained by the hydrazine (being more toxic than OBSH) formed from hydrolysis during the toxicity testing, it is considered a conservative approach to make a read-across of ecotoxicity data from OBSH to p-TSH, and the toxicity of the target substance is likely to be overestimated."*

You predict the properties of the Substance using a read-across hypothesis which assumes that different compounds have the same type of effects. You predict that the properties of your Substance are based on a worst-case approach.

You have not established a reliable basis for predicting ecotoxicological properties for the following reasons:

i. Read-across hypothesis

A read-across hypothesis needs to be provided, establishing why a prediction for a toxicological or ecotoxicological property is reliable. This hypothesis should be based on recognition of the structural similarities and differences between the source substance(s) and your Substance[8]. It should explain why the differences in the chemical structures should not influence the toxicological/ ecotoxicological properties or should do so in a regular pattern.

Your read-across hypothesis is that the similarity in chemical structure and in some of the physicochemical, (eco)toxicological properties between the source substance(s) and the Substance is a sufficient basis for predicting the properties of the Substance for other endpoints.

Similarity in chemical structure and similarity of some of the physicochemical and (eco)toxicological properties does not necessarily lead to predictable or similar ecotoxicological properties in other endpoints. Additionally, there are differences in the structures and in the physico-chemical properties between the source substance and the Substance, which leads to differences in fate (e.g. different hydrolysis rate and bioavailability) and may impact the toxicity. However, you have not considered the impact of these differences on the prediction.

Therefore, you have not provided a well-founded hypothesis to establish a reliable prediction for the ecotoxicological properties.

ii. Supporting information

[8] ECHA Guidance R.6

Annex XI, Section 1.5 of the REACH Regulation states that "*physicochemical properties, human health effects and environmental effects or environmental fate may be predicted from data for reference substance(s)*". For this purpose "*it is important to provide supporting information to strengthen the rationale for the read-across*"[9]. The set of supporting information should allow to verify the crucial aspects of the read-across hypothesis and establish that the properties of the Substance can be predicted from the data on the source substance(s).

Supporting information must include for example bridging studies of comparable experimental design and duration for the Substance and the source substance(s).

As indicated above, your read-across hypothesis is based on the assumption that the structurally similar substances cause the same type of effect(s). In this context, relevant, reliable and adequate information allowing to compare the properties of the Substance and of the source substance(s) is necessary to confirm that both substance cause the same type of effects and your worst-case hypothesis.

In order to substantiate your hypothesis of the worst case, you provide in the dossier:

- Short-term (*Daphnia*, fish and algae, all using static or semi-static study design) and long-term aquatic toxicity studies (*Daphnia* (semi static design) and fish (flow through design)) for the source substance OBSH. The short-term studies are listed under the relevant information requirement sections A.1, A.2 and B.4 below.
- Short-term fish and short-term *Daphnia* studies with hydrazine, the common hydrolysis product of source and target substances.

Furthermore, in the read-across justification document you report:

- Hydrolysis half-lives of 7.9h for the source substance and 39h for the Substance, at pH 7 and 20°C.
- Aquatic toxicity results for hydrazine (common hydrolysis product). Aquatic toxicity results for the non-common hydrolysis products of source and target substances, which show low aquatic hazards.

You further indicate that "*the observed toxicity of OBSH is partly explained by the hydrazine (being more toxic than OBSH) formed from hydrolysis during the toxicity testing*".

However, the information you provided cannot be used to support your hypothesis, for the following reasons:

Firstly, the hydrolysis of the source substance is not immediate. As a consequence and due to the test designs, both the parent and the common hydrolysis product hydrazine were present in the test solutions during the studies with OBSH. Specifically, both the parent and the hydrolysis products were present in the test solutions of the static studies due to the test duration, in the semi static due to the time intervals of the test solutions renewal being higher than hydrolysis half-life. In the flow through studies the concentration of the parent was stable.

Since aquatic organisms were exposed to both OBSH and hydrazine, it is not possible to know the contribution of the parent and that of hydrazine to the overall effects observed in the aquatic toxicity studies. In the long-term fish study with flow through design and constant concentration of the OBSH parent, the source substance OBSH was clearly hazardous (NOEC 0.09 mg/L). Your claim of the common hydrolysis product hydrazine being a major contributor to toxicity is hence not supported by the data. The contribution of the parent therefore must

[9] ECHA Guidance R.6, Section R.6.2.2.1.f

be considered. As given above there are differences in the structures and in the physico-chemical properties between the (parent) source substance and the Substance and you have not considered the impact of these differences on the prediction.

Secondly, the data set reported in the technical dossier does not include any study with the Substance for the endpoints under consideration. Furthermore, there are differences between target and source substances in hydrolysis rates and hence in the stability of the parent substances in test solutions. Therefore, it is not possible to know if exposure to the Substance, that hydrolyses more slowly, would give similar results as the studies with the source. Furthermore, according to ECHA Guidance R.7b ECETOC (2003) in aquatic testing and the TGD recommend to test parent substance with a half-life as low as 12 h. As the reported hydrolysis half-life of the Substance is 39h (pH 7, 20°C), the toxicity of the parent must be considered.

Due to the above, it is not possible to directly compare the properties of target and source substances.

In conclusion, the provided supporting information does not allow to confirm that both substance cause the same type of effects and that predictions based on worst-case would be reliable.

iii. Relevance of supporting information

According to the ECHA Guidance[10] "*it is important to provide supporting information to strengthen the rationale for the read-across approach. Thus, in addition to the property/endpoint being read-across, it is also useful to show that additional properties, relevant to the endpoint, are also (qualitatively or quantitatively) similar between the source and target chemicals*".

In order to support your claim that your Substance and source substance(s) have similar properties for the endpoints under consideration in the read-across approach, you refer to their toxicity to microorganism properties.

Whilst this data set suggests that the Substance may be less toxic to aquatic microorganisms than the source substance, these studies do not inform on the aquatic toxicity properties of the target and source substances to fish, aquatic invertebrates and aquatic plants.

Accordingly, this information is not considered as relevant to support prediction of all the endpoints under consideration.

C. Conclusions on the read-across approach

You have not established that relevant properties of the Substance can be predicted from data on the source substance(s). Your use of a read-across approach under Annex XI, section 1.5. is rejected.

[10] ECHA Guidance R.6, Section R.6.2.2.1.f

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

1. Short-term toxicity testing on aquatic invertebrates

Short-term toxicity testing on aquatic invertebrates is a standard information requirement at Annex VII of REACH.

You have adapted this information requirement by using a Grouping of substance and read-across approach under Annex XI, section 1.5. and you have provided in your dossier the following study record(s):

i. SIDS Initial Assessment Report for SIAM 22, 2006 (2004), key study, according to OECD TG 202 with the analogue substance 4,4'-oxydi(benzenesulphonohydrazide) (OBSH), EC No. 201-286-1 (CAS No. 80-51-3);

ii. SIDS Initial Assessment Report for SIAM 22, 2006 (2005), supporting study, according to OECD TG 202 with the analogue substance OBSH.

We have assessed this information and identified the following issue(s).

The studies listed in i. and ii. above were conducted with the analogue substance OBSH. However, as explained in the Appendix on general considerations your adaptation according to Annex XI, Section 1.5 is rejected.

2. Growth inhibition study aquatic plants

Growth inhibition study aquatic plants is a standard information requirement at Annex VII of REACH.

You have adapted this information requirement by using a Grouping of substance and read-across approach under Annex XI, section 1.5. and you have provided in your dossier the following study record(s):

i. SIDS Initial Assessment Report for SIAM 22, 2006 (2004), key study, according to OECD TG 201 with the analogue substance 4,4'-oxydi(benzenesulphonohydrazide) (OBSH), EC No. 201-286-1 (CAS No. 80-51-3);

ii. SIDS Initial Assessment Report for SIAM 22, 2006 (2005), supporting study, according to OECD TG 201 with the analogue substance OBSH.

We have assessed this information and identified the following issue(s).

The studies listed in i. and ii. above were conducted with the analogue substance OBSH. However, as explained in the Appendix on general considerations your adaptation according to Annex XI, Section 1.5 is rejected.

Appendix B: Reasons to request information required under Annex VIII of REACH

1. In vivo mammalian alkaline comet assay or Transgenic rodent somatic and germ cell gene mutation assays

Under Annex VIII to REACH, the performance of an appropriate *in vivo* somatic cell genotoxicity study must be considered if there is a positive result in any of the *in vitro* genotoxicity studies in Annex VII or VIII.

You have provided an *in vivo* mammalian erythrocyte micronucleus test according to OECD TG 474 (OECD SIDS Assessment Report for SIAM 22, 2006 (2000)), performed with the analogue substance 4,4'-oxydi(benzenesulphonohydrazide) (OBSH), EC No. 201-286-1 (CAS No. 80-51-3), as key study.

We have assessed this information and identified the following issues:

You have adapted the information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5 .

As explained in the Appendix on Reasons common to several requests your adaptation is rejected. In addition, the following endpoint-specific deficiency has been identified in your read-across adaptation:

In order to be appropriate, according to ECHA Guidance R.7a, the *in vivo* somatic cell genotoxicity study must address the specific concern raised by the *in vitro* positive result.

Your dossier contains a negative result for the *in vitro* mammalian chromosome aberration test (Blakey 1992; OECD TG 473, with the Substance), but positive results for the *in vitro* gene mutation study in bacteria (Seifried 2006, Blakey 1992; OECD TG 471, with the Substance) and *in vitro* gene mutation study in mammalian cells (Seifried 2006; OECD TG 476, with the Substance). The positive results raise the concern for gene mutation.

However, the *in vivo* study provided is not addressing the gene mutation concern raised by the *in vitro* data. Therefore, the provided *in vivo* test is not appropriate.

ECHA considers that an appropriate *in vivo* follow up mutagenicity study is necessary to address the concern identified *in vitro*.

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

Test selection

According to the ECHA Guidance Chapter R.7a[11], the transgenic rodent somatic and germ cell gene mutation assays ("TGR assay", OECD TG 488) and the *in vivo* mammalian alkaline comet assay ("comet assay", OECD TG 489) are suitable to follow up a *positive in vitro* result on gene mutation.

[11] ECHA Guidance Chapter R.7a, Section R.7.7.6.3

Test design

Comet assay:
In case you decide to perform the comet assay according to the test method OECD TG 489, the test must be performed in rats. Having considered the anticipated routes of human exposure and adequate exposure of the target tissue(s) performance of the test by the oral route is appropriate.

In line with the test method OECD TG 489, the test must be performed by analysing tissues from liver as primary site of xenobiotic metabolism, glandular stomach and duodenum as sites of contact. There are several expected or possible variables between the glandular stomach and the duodenum (different tissue structure and function, different pH conditions, variable physico-chemical properties and fate of the Substance, and probable different local absorption rates of the Substance and its possible breakdown product(s)). In light of these expected or possible variables, it is necessary to analyse both tissues to ensure a sufficient evaluation of the potential for genotoxicity at the site of contact in the gastro-intestinal tract.

TGR assay:
In case you decide to perform the TGR assay, according to the test method EU B.58/OECD TG 488, the test must be performed in transgenic mice or rats and the test substance is usually administered orally.

According to the test method EU B.58/OECD TG 488, the test must be performed by analysing tissues from liver as slowly proliferating tissue and primary site of xenobiotic metabolism, glandular stomach and duodenum as rapidly proliferating tissue and site of direct contact. There are several expected or possible variables between the glandular stomach and the duodenum (different tissue structure and function, different pH conditions, variable physico-chemical properties and fate of the Substance, and probable different local absorption rates of the Substance and its possible breakdown product(s)). In light of these expected or possible variables, it is necessary to analyse both tissues to ensure a sufficient evaluation of the potential for mutagenicity at the site of contact in the gastro-intestinal tract. However, duodenum must be stored (at or below −70 °C) until the analysis of liver and glandular stomach is completed; the duodenum must then be analysed only if the results obtained for the glandular stomach and for the liver are negative or inconclusive.

Germ cells

Comet
You may consider to collect the male gonadal cells collected from the seminiferous tubules (as described by e.g. O'Brien *et al.*[12]) in addition to the other aforementioned tissues, as it would optimise the use of animals. You can prepare the slides for male gonadal cells and store them for up to 2 months, at room temperature, in dry conditions and protected from light. Following the generation and analysis of data on somatic cells, you should consider analysing the slides prepared with gonadal cells. This type of evidence may be relevant for the overall assessment of possible germ cell mutagenicity including classification and labelling according to the CLP Regulation.

[12] O'Brien, J.M., Beal, M.A., Gingerich, J.D., Soper, L., Douglas, G.R., Yauk, C.L., Marchetti, F. (2014) Transgenic Rodent Assay for Quantifying Male Germ Cell Mutant Frequency. J. Vis. Exp. (90), e51576, doi:10.3791/51576

TGR
You may consider to collect the male germ cells at the same time as the other tissues, in order to limit additional animal testing. According to the OECD 488 the tissues (or tissue homogenates) can be stored under specific conditions and used for DNA isolation for up to 5 years (at or below −70 ºC). Following the generation and analysis of data on somatic cells, you should consider analysing the collected germ cells. This type of evidence may be relevant for the overall assessment of possible germ cell mutagenicity including classification and labelling according to the CLP Regulation.

2. Short-term repeated dose toxicity (28 days)

A Short-term repeated dose toxicity study (28 days) is a standard information requirement in Annex VIII to REACH.

You have provided the following key and supporting studies in your dossier:

i. OECD SIDS Assessment Report for SIAM 22, , 2006 (2001), key study, according to OECD TG 407 with the analogue substance 4,4'-oxydi(benzenesulphonohydrazide) (OBSH), EC No. 201-286-1 (CAS No. 80-51-3);

ii. [redacted] 2017, key study, according to OECD TG 408 with the analogue substance OBSH;

iii. OECD SIDS Assessment Report for SIAM 22, 2006 (2001), key study, according to OECD TG 421 with the analogue substance OBSH;

iv. OECD SIDS Assessment Report for SIAM 22, 2006 (2001), key study, according to OECD TG 422 with the analogue substance OBSH;

v. [redacted] 1989, supporting study, according to OECD TG 407 (1981 version, with deviations, performed with 14 days of dosing) with the Substance.

We have assessed this information and identified the following issues:

You have adapted the information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. The studies listed in i.-iv. above were conducted with the analogue substance OBSH.

As explained in the Appendix on Reasons common to several requests your adaptation is rejected.

To be considered compliant and enable concluding whether the Substance has dangerous properties and supports the determination of the No-Observed Adverse Effect Level (NOAEL), a study has to meet the requirements of OECD TG 407. The key parameters of this test guideline include the dosing of the Substance daily for a period of 28 days until the scheduled termination of the study.

Study v. above does not have the required exposure duration of 28 days as required in OECD TG 407, because you indicated an exposure duration of 14 days.

Therefore, the information requirement is not fulfilled.

When there is no information available neither for the 28-day repeated dose toxicity endpoint (EU B.7, OECD TG 407), nor for the screening study for reproductive/ developmental toxicity

(OECD TG 421 or TG 422), the conduct of a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) is preferred to ensure that unnecessary animal testing is avoided. Such an approach offers the possibility to avoid carrying out a 28-day study according to OECD TG 407, because the OECD TG 422 can at the same time fulfil the information requirement of REACH Annex VIII, 8.6.1 and that of REACH Annex VIII, 8.7.1.[13]

Specifications for the study design

A study according to the test method EU B.64/OECD TG 422 must be performed in rats with oral[13] administration of the Substance as requested in B.3.

3. Screening for reproductive/developmental toxicity

A Screening for reproductive/developmental toxicity study (test method: EU B.63/OECD TG 421 or EU B.64/OECD TG 422) is a standard information requirement under Annex VIII to REACH, if there is no evidence from analogue substances, QSAR or *in vitro* methods that the Substance may be a developmental toxicant.

You have provided the following key studies in your dossier:

i. OECD SIDS Assessment Report for SIAM 22, 2006 (2001), key study, according to OECD TG 421 with the analogue substance OBSH;

ii. OECD SIDS Assessment Report for SIAM 22, 2006 (2005), key study, according to OECD TG 422 with the analogue substance OBSH;

iii. [redacted] 2017, key study, according to OECD TG 414 with the analogue substance OBSH.

We have assessed this information and identified the following issues:

You have adapted the information requirement by using a Grouping of substances and read-across approach under Annex XI, Section 1.5. The studies listed in i.-iii. above were conducted with the analogue substance OBSH.
As explained in the Appendix on Reasons common to several requests your adaptation is rejected.

Therefore, the information requirement is not fulfilled and a Screening for reproductive/developmental toxicity study is required.

For the reasons explained in B.2, the conduct of a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (OECD TG 422) is preferred to ensure that unnecessary animal testing is avoided.

Specifications for the study design

A study according to the test method EU B.64/OECD TG 422 must be performed in rats with oral[13] administration of the Substance.

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

4. Short-term toxicity testing on fish

Short-term toxicity testing on fish is a standard information requirement at Annex VIII of REACH.

You have adapted this information requirement by using a Grouping of substance and read-across approach under Annex XI, section 1.5. and you have provided in your dossier the following study record(s):

i. SIDS Initial Assessment Report for SIAM 22, 2006 (2000), key study, according to OECD TG 203 with the analogue substance 4,4'-oxydi(benzenesulphonohydrazide) (OBSH), EC No. 201-286-1 (CAS No. 80-51-3);

ii. SIDS Initial Assessment Report for SIAM 22, 2006 (2004), supporting study, according to OECD TG 203 with the analogue substance OBSH.

We have assessed this information and identified the following issue(s).

The studies listed in i. and ii. above were conducted with the analogue substance OBSH. However, as explained in the Appendix on general considerations your adaptation according to Annex XI, Section 1.5 is rejected.

Appendix C: 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[14].

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[15].

[14] https://echa.europa.eu/practical-guides
[15] https://echa.europa.eu/manuals

Appendix D: 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 7 August 2019.

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

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

In your comments you mentioned an undergoing change of the Only Representative. As this matter does not affect the decision making process of this decision, ECHA dealt with this matter in a separate communication.

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 E: List of references - ECHA Guidance[16] 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)[17]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[17]

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.

[16] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[17] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across

OECD Guidance documents[18]

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.

[18] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Appendix F: 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]
[redacted]	[redacted]	[redacted]
[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.