ECHA
EUROPEAN CHEMICALS AGENCY

Helsinki, 13 January 2017

Addressee: [redacted]

Decision number: CCH-D-2114350947-38-01/F
Substance name: sodium 3-nitrobenzenesulphonate
EC number: 204-857-3
CAS number: 127-68-4
Registration number: [redacted]
Submission number: [redacted]
Submission date: 25.11.2013
Registered tonnage band: 100-1000T

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. **In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.; test method: Bacterial reverse mutation test, EU B.13/14. / OECD TG 471) using one of the following strains: E.coli WP2 uvrA, or E.coli WP2 uvrA (pKM101), or S. typhimurium TA102 with the registered substance;**

2. **In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.; test method: OECD TG 476 or TG 490) with the registered substance;**

3. **Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.; test method: EU B.26./OECD TG 408) in rats with the registered substance;**

4. **Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.; test method: OECD [421/422]) in rats, oral route with the registered substance;**

5. **Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.; test method: EU B.31./OECD TG 414) in a first species (rat or rabbit), oral route with the registered substance.**

You may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI of the REACH Regulation. In order to ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring and conforming to the appropriate rules in the respective Annex, and an adequate and reliable documentation.

You are required to submit the requested information in an updated registration dossier by **22 July 2019**. You shall also update the chemical safety report, where relevant. The timeline has been set to allow for sequential testing.

The reasons of this decision are set out in Appendix 1. The procedural history is described in Appendix 2. Advice and further observations are provided in Appendix 3.

Who performs the testing

Based on Article 53 of the REACH Regulation, you are requested to inform ECHA who will carry out the study/ies on behalf of all Registrant(s) within 90 days. Instructions on how to do this 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, shall 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 Ofelia Bercaru, Head of Unit, Evaluation E3

[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

0. Adaptation approach

Article 13(1) of the REACH Regulation stipulates that information on intrinsic properties of substances may be generated by means other than tests, provided that the conditions set out in Annex XI are met.

In that respect, ECHA notes that you have adapted the standard information requirements for the following endpoints addressed in the present decision with weight of evidence approaches:

- Sub-chronic toxicity study (90 day) repeated dose toxicity study (Annex IX, Section 8.6.2.)
- Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)
- Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

Section 1.2 of the Annex XI of the REACH Regu

lation sets out the prerequisites of weight of evidence approaches followingly:

> "*There may be sufficient weight of evidence from several independent sources of information leading to the assumption/conclusion that a substance has or has not a particular dangerous property, while the information from each single source alone is regarded insufficient to support this notion*".

Therefore, an evidence based approach involves an assessment of the relative values/weights of different pieces of the available information that have been retrieved and gathered in previous steps. To this end, a value needs to be assigned to each piece of information. These weights/values can be assigned either in an objective way by using a formalised procedure or by using expert judgement. The weight given to the available evidence depends on factors such as the quality of the data, consistency of results, nature and severity of effects and relevance of the information for the given regulatory endpoint.

In the present case, the weight of evidence approaches you propose are themselves based on sources of information such as (Q)SARs and grouping approaches. These sources of information are themselves adaptations, which are described in respective sections of Annex XI and subject to specific conditions. The fulfillment of all or parts of these conditions determines the quality and reliability of these sources of information for assuming or concluding that a substance has or has not a particular dangerous property.

However, ECHA notes systematic deficiencies regarding the conformity of these sources of information with the conditions set out in Annex XI of the REACH Regulation. These deficiencies are such that they call into question the quality and reliabity of these sources of information as valid pieces of a weight of evidence argumentation.

The following addresses the invalidity of these sources of information for the purpose of justifying a weight of evidence approach.

ECHA notes that for these information requirements you have provided information on analogue substances identified from the OECD QSAR toolbox. More specifically, you have used these analogues as sources of information as part of a weight of evidence argumentation. Even though you have reported this information as "QSAR" in the field study result type in IUCLID, on the basis of the indications included in the corresponding prediction report, ECHA understands that these arguments do not refer to QSAR models but rather to read-across and category approaches. Therefore, the quality and reliability of such sources of information shall be assessed against the conditions applying to read-across and category approaches.

Category and read-across approach

The member substances of the category referred to exhibit structural differences such as presence of additional functional groups. The category justification document does not contain information on the allowed structural differences within the category, thereby creating uncertainty on the boundaries of this category. Should the structural differences observed among the category members be allowed within the category, you did not provide information on how these structural differences may or may not affect the prediction of properties within the category, as a condition of Annex XI, 1.5. of the REACH Regulation. Further, the absence of mechanistic alert has been used to refine the selection of category members. ECHA is of the opinion that these selection criteria do not constitute a basis on which the properties of the registered substance can be established from the data on other category members. The absence of predicted activity on these mechanisms does not preclude that other pathways and mechanisms of toxicity may be activated. This is particularly relevant in the context of the prediction of properties for particularly complex higher tier endpoints for which the mechanisms of toxicity are many and largely unknown. The selection of members of the category on the basis of absence of mechanistic alerts appears to suggest a bias in the prediction of the properties of the registered substance. Therefore, ECHA is of the opinion that the limits of the category have not been unambiguously defined; that a structure-activity relationship is missing from the category as currently documented; and that the impact of the structural differences among the category members on the prediction of properties within the category has not been assessed and reported.

For the reasons listed above, ECHA considers that this read-across and category approach does not allow a reliable prediction of the properties of the registered substance for the endpoints under consideration. As a consequence, ECHA is of the opinion that this information, as currently provided, cannot be regarded as relevant and reliable information in the context of this weight of evidence approach on the dangerous properties of the registered substance. Further endpoint specific considerations are provided in the appropriate sections below.

1. In vitro gene mutation study in bacteria (Annex VII, Section 8.4.1.)

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

An "*In vitro* gene mutation study in bacteria" is a standard information requirement as laid down in Annex VII, Section 8.4.1. 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.

According to Article 13(3) of the REACH Regulation, tests required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods recognised by the Commission or ECHA.

Other tests may be used if the conditions of Annex XI are met. More specifically, Section 1.1.2 of Annex XI provides that existing data on human health properties from experiments not carried out according to GLP or the test methods referred to in Article 13(3) may be used if the following conditions are met:

(1) Adequacy for the purpose of classification and labelling and/or risk assessment;
(2) Adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3);
(3) Exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3) if exposure duration is a relevant parameter; and
(4) adequate and reliable documentation of the study is provided.

According to paragraph 13 of the current OECD TG 471 test guideline (updated 1997) at least five strains of bacteria should be used: S. typhimurium TA1535; TA1537 or TA97a or TA97; TA98; TA100; S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101). This includes four strains of S. typhimurium (TA1535; TA1537 or TA97a or TA97; TA98; and TA100) that have been shown to be reliable and reproducibly responsive between laboratories. These four S. typhimurium strains have GC base pairs at the primary reversion site and it is known that they may not detect certain oxidising mutagens, cross-linking agents and hydrazines. Such substances may be detected by E.coli WP2 strains or S. typhimurium TA102 which have an AT base pair at the primary reversion site.

You have provided a test marked as weight of evidence from the year 1989 according to OECD TG 471 and GLP with an assigned reliability score of 2. The test used four different strains of S. typhimurium TA 1535, TA 1537, TA 98 and TA 100 and it did not include tests with strains S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101). In addition, you submitted a test from the year 1994 also marked as weight of evidence that did not follow any guideline with an assigned reliability score of 2. No information was provided on the strains used in this test. However, since these test were conducted, significant changes have been made to OECD TG guideline 471 so that additionally testing with S. typhimurium TA102 or E. coli WP2 uvrA or E. coli WP2 uvrA (pKM101) is now required. Therefore, the provided study does not meet the current guidelines, nor can it be considered as providing equivalent data according to the criteria in Annex XI, 1.1.2. of the REACH Regulation.

ECHA concludes that a test using *E. coli* WP2 uvrA, or *E. coli* WP2 uvrA (pKM101), or *S. typhimurium* TA102 has not been submitted and that the test using one of these is required to conclude on *in vitro* gene mutation in bacteria.

In your comments to the draft decision, you stated the following "Japanese study equivalent to OECD 471 study is presented within the dossier and results confirms that substance is not genotoxic in nature thus this study need not to be conducted for the above mentioned substance."

ECHA however notes that this study as well as its shortcomings (absence of testing using *E. coli* WP2 uvrA, or *E. coli* WP2 uvrA (pKM101), or *S. typhimurium* TA102) is addressed above. Your comments do not address these shortcomings.

Therefore, your adaptation of the information requirement is rejected.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA considers that the bacterial reverse mutation test (test method EU B.13/14. / OECD TG 471) is appropriate to address the standard information requirement of Annex VII, Section 8.4.1. of the REACH Regulation.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to complete following information derived with the registered substance subject to the present decision: Bacterial reverse mutation test (test method: EU B.13/14. / OECD TG 471) using one of the following strains: E. coli WP2 uvrA, or E. coli WP2 uvrA (pKM101), or S. typhimurium TA102.

2. In vitro gene mutation study in mammalian cells (Annex VIII, Section 8.4.3.)

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

An "*In vitro* gene mutation study in mammalian cells" is an information requirement as laid down in Annex VIII, Section 8.4.3. of the REACH Regulation, "if a negative result in Annex VII, Section 8.4.1. and Annex VIII, Section 8.4.2." is obtained.

ECHA notes that the registration dossier contains negative results for both these information requirements, although information is currently missing on the 5th strain in the *in vitro* gene mutation study in bacteria, as described above. Therefore, adequate information *on in vitro* gene mutation in mammalian cells needs to be present in the technical dossier for the registered substance to meet this information requirement provided that the study requested under request 1 has negative results.

You have not provided any study record of an *in vitro* gene mutation study in mammalian cells in the dossier that would meet the information requirement of Annex VIII, Section 8.4.3.

The technical dossier does not contain an adaptation in accordance with column 2 of Annex VIII, Section 8.4.3. or with the general rules of Annex XI for this standard information requirement.

In your comments to the draft decision, you stated the following "The data from OECD 474 in vivo genetic toxicity study is present within the dossier which confirms the substance is not genetically toxic substance so we would request ECHA to kindly consider to waive of this information requirement."

ECHA notes, however, that the available study is an in vivo micronucleus study done according to OECD TG 474. An in vivo micronucleus study aims to detect cytogenetic damage (damage to chromosomes or the mitotic apparatus), whereas an in vitro gene mutation study in mammalian cells aims to detect gene mutations. Therefore, these two studies address different aspects of mutagenicity, and the in vivo micronucleus study is not appropriate to address the gene mutation study in mammalian cells. Therefore, ECHA considers that there is a data gap for this endpoint.

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.

ECHA considers that the *in vitro* mammalian cell gene mutation tests using the *Hprt* and *xprt* genes (OECD TG 476) and the *in vitro* mammalian cell gene mutation tests using the thymidine kinase gene (OECD TG 490) are appropriate to address the standard information requirement of Annex VIII, Section 8.4.3.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: *In vitro* mammalian cell gene mutation test (test method: OECD TG 476 *or* OECD TG 490) provided that the study requested under 1 has negative results.

3. Sub-chronic toxicity study (90-day), oral route (Annex IX, Section 8.6.2.)

Pursuant to Articles 10(a) and 12(1) of the REACH Regulation, a technical dossier registered at 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annexes VII to IX of the REACH Regulation. The information to be generated for the dossier must fulfil the criteria in Article 13(4) of the same regulation.

A "sub-chronic toxicity study (90 day)" is a standard information requirement as laid down in Annex IX, Section 8.6.2. 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 X 1.2 (Weight of evidence). In support of this, you have included three endpoint study records in your IUCLID dossier for repeated dose toxicity, marked as weight of evidence. These endpoint study records are for:

1) A 2-year chronic toxicity study (Wernick et al, 1975), on beagle dogs, by oral feed, performed on a hair dye formulation that is composed of [redacted]% of the registered substance, while the remainder ([redacted]%) is composed of other substances. The doses in the study were as follows: 0, 19.5, and 97.5 mg/kg/bw. The overall conclusion of the study is that no adverse effects were observed, and you have set the NOAEL as the top dose 97.5mg/kg/bw. The number of animals used was 6 males and 6 females per dose group
2) A QSAR adaptation using the OECD QSAR toolbox. The NOAEL is predicted to be 435 mg/kg/bw.
3) A 28 day repeated dose toxicity study ([redacted], 1998), on rats, by oral gavage, done on the registered substance. The doses in the study were as follows: 0, 100, 300 and 1000 mg/kg/bw. The NOEL was assigned as 300 mg/kg/bw. The number of animals used was 10 males and 10 females for both control and 1000 mg/kg/bw groups, and 5 males and 5 females for the 100 and 300 mg/kg/bw groups.

However, ECHA notes that none of the studies individually is sufficient to fulfil the requirements of a 90 day study for the reasons presented below. Furthermore, ECHA notes that your adaptation does not meet the general rule for adaptation of Annex XI; Section 1.2. (Weight of evidence) for the following reasons:

- **The chronic toxicity study**

While this study covers exposure duration longer than 90 days, it has been performed on a hair dye formulation containing [redacted]% of the registered substance. The top dose in this study was 97.5 mg/kg/bw of the formulation, which equates to an exposure of 2.2 mg/kg/bw of the registered substance. No effects were observed in the study you have set the NOAEL as 97.5 mg/kg/bw.

The dose level of the registered substance is considered too low to allow for conclusions to be drawn on the potential effects of the registered substance in a 90 day repeated dose toxicity study. In addition, the number of animals per dose group is significantly lower than the number required in a 90-day study (6 vs. 10 animals per sex per dose group). Therefore, the sensitivity of this study is much lower than that of a 90-day study.

- **The QSAR study**

You have provided information on analogue substances obtained from the OECD QSAR toolbox. As indicated above, ECHA has assessed this line of evidence as a read-across approach. You have attached a prediction report to the endpoint study record. This report provides information on the method used for identifying the analogue substances used for the prediction and reports a dose descriptor of 435 mg/kg/day for the registered substance. You listed in the prediction report a series of "referential boundaries" presenting required structural elements for the analogue substances, defined as category members. However ECHA observes that you did not clearly establish, as part of an endpoint-specific read-across hypothesis, how the presence of these structural elements among the category members can be linked with the possibility for predicting the properties of the registered substance from data on the category members as required by Annex XI, 1.5. of the REACH Regulation. Further, ECHA notes that no information on the allowed structural differences among the category members is included in the prediction report.

According to information provided in the appendix 1 of the report, significant structural differences exist among the analogue substances. The impact of these considerable differences in the chemical structures of the category members on the possibility to predict properties of the registered substance has not been accounted for in the read-across hypothesis.

The prediction report indicates that the prediction has been established for the endpoint "*LOEL, NOEL, NOEL calculated*" on the basis of "*recalculated experimental data*". No information on the scope of the investigations and the duration of the source studies conducted with the analogue substances is provided so their relevance for the information expected to be provided to fulfil the information requirement for a 90-day repeated dose toxicity study cannot be determined. Therefore, in the absence of robust study summaries presenting the details of the study protocols and demonstrating the validity of these assays, the validity of the prediction cannot be determined.

It remains unclear whether the predicted value of 435 mg/kg/day should be regarded as a LOEL, NOEL or NOAEL for the registered substance. No details on the nature of the recalculations mentioned in the prediction report have been provided. Further, the information included in the report suggests that the data used to establish the prediction has been collected from studies conducted in different species, i.e. rats and mice. No information describing how the potential interspecies differences between rats and mice have been accounted for has been reported.

For all the reasons listed above, ECHA considers that this read-across approach does not allow a reliable prediction of the properties of the registered substance for the endpoint under consideration. As a consequence, ECHA is of the opinion that this information, as currently provided, cannot be regarded as relevant and reliable information in the context of this weight of evidence approach on the dangerous properties of the registered substance.

- **The 28 day repeated dose toxicity study**

This study does not provide adequate coverage of the relevant parameters of a 90 day study. Furthermore, it does not cover the same duration as a 90 day study. Therefore, it provides insufficient evidence, even if combined with the above two studies, that the substance would not have an effect in a 90 day study. In addition, the number of animals per dose group for the 100 and 300 mg/kg/bw groups is significantly lower than the number required in a 90-day study (10 animals per sex per dose group). Therefore, the sensitivity of this study is much lower than that of a 90-day study.

As explained above, the individual studies themselves are not sufficient to fulfil the information requirements. In addition, you have not provided an argument in his dossier for why these sources of information lead to the assumption/conclusion that the substance has or has not a particular dangerous property, given that the information from the individual sources (as analysed above) are insufficient to support this notion.

In your comments to the draft decision, you indicated that a 28 day repeated dose toxicity study from Japan is available, and this study shows no effects, and the NOAEL was set at 1000 mg/kg/bw. Furthermore, you indicated that the dossier contains a 2 year chronic toxicity study on dogs via the oral route.

However, ECHA already addressed these two studies, as well as their deficiencies, above. Your comments do not bring any new information, nor do they address any of these deficiencies. Instead, they reiterate what is already available in the dossier.

ECHA considers that the Weight of Evidence approach does not meet the criteria for weight of evidence in accordance to Annex XI, 1.2. This is because even when taken together, the studies do not cover all the parameters of a 90 day repeated dose toxicity study. The 28 day study is not of adequate duration and does not cover the parameters of a 90 day study. The chronic toxicity study has not been performed on the registered substance, and the doses (as described above) do not allow for any conclusions to be drawn on the properties of the registered substance, and the QSAR study (as described above) does not provide relevant and reliable information in the context of a weight of evidence approach.

Therefore, your adaptation of the information requirement is rejected.

As explained above, the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

ECHA has evaluated the most appropriate route of administration for the study. Based on the information provided in the technical dossier and/or in the chemical safety report, ECHA considers that the oral route - which is the preferred one as indicated in ECHA Guidance on information requirements and chemical safety assessment (version 4.1, October 2015) Chapter R.7a, section R.7.5.4.3 - is the most appropriate route of administration. More specifically, the substance is a solid with particle size distribution (granulometry) in the range of 75 micrometer to 600 micrometer. The majority of the particles are found to be more than 150 (47.00 %) - 75 (19.77%) micrometer in size. The substance has a large particle size and there is no significant proportion (>1% on weight basis) of particles of inhalable size (MMAD < 50 µm). Hence, the test shall be performed by the oral route using the test method EU B.26./OECD TG 408.

According to the test method EU B.26./OECD TG 408 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Repeated dose 90-day oral toxicity study (test method: EU B.26./OECD TG 408) in rats.

4. Screening for reproductive/developmental toxicity (Annex VIII, Section 8.7.1.)

"Screening for reproductive/developmental toxicity" (test method OECD TG 421 or 422) is a standard information requirement as laid down in Annex VIII, Section 8.7.1. of the REACH Regulation if there is no evidence from available information on structurally related substances, from (Q)SAR estimates or from *in vitro* methods that the substance may be a developmental toxicant. No such evidence is presented in the dossier.

Therefore, adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

You have not provided any study record of a screening for reproductive/developmental toxicity in the dossier that would meet the information requirement of Annex VIII, Section 8.7.1.

Instead, in the technical dossier you have provided study records for the following studies:

1) A "one generation" study (Wernick, 1975), performed on rats, with no particular guideline cited. The study was not performed on the registered substance, but on a formulation where the concentration of the registered substance is 2.25% of the formulation. The doses used in the study were 0, 97.5 and 390 mg/kg/bw of the formulation. This means that the top dose administered of the registered substance was 8.775 mg/kg/bw. No effects on reproductive parameters was observed in this study. The NOAEL reported is 390 mg/kg/bw for the hair dye formulation, which is equivalent to 8.775 mg/kg/bw of the registered substance. (one generation on rats, 'study 1')

2) A "one generation" study (Wernick, 1975) performed on New Zealand white rabbits. No particular guideline was cited. Similarly to study 1 above, the test material is a hair dye formulation, where the registered substance represents 2.25% of the formulation. The doses (of the formulation) in the study were 0, 19.5 and 97.5 mg/kg/bw. No effects on reproductive toxicity were observed in this study. The NOAEL reported for this study is 97.5 mg/kg/bw for the hair dye formulation, which is equivalent to 2.2 mg/kg/bw of the registered substance. (one generation on rabbits, 'study 2')

3) A QSAR study done using the OECD QSAR toolbox 3.1. The predicted NOAEL for reproductive toxicity is 162 mg/kg/bw.

However, ECHA notes that none of the studies individually is sufficient to fulfil the requirements of a screening study for reproductive/developmental toxicity for the reasons presented below. Furthermore, ECHA notes that your adaptation does not meet the general rule for adaptation of Annex XI; Section 1.2. (Weight of evidence) for the following reasons:

- **The one generation studies 1 and 2**

In the first and second studies, the doses of the registered substance are too low to allow for a conclusion on the hazards of the registered substance in this study. Therefore, these two studies on their own are not sufficient to fulfil the information requirement. Furthermore, given the low dose of the registered substance, these studies cannot be considered to be relevant studies in a Weight of Evidence case as the dose doesn't allow for any conclusions on the properties of the registered substance.

- **The QSAR study**

You have provided information on analogue substances obtained from the OECD QSAR toolbox. As indicated above in section 0 above, ECHA has assessed this line of evidence as a read-across approach. You have attached a prediction report to the endpoint study record. This report provides information on the method used for identifying the analogue substances used for the prediction and reports a *"Prediction of adult and offspring), females), LOAEL, LOAEL (offspring general toxicity), LOAEL systemic, LOAEL(general tox., LOAEL(general toxicity, males), NOAEL, NOAEL (adult general toxicity), NOAE".*

You listed in the prediction report a series of "referential boundaries" presenting required structural elements for the analogue substances, defined as category members. However ECHA observes that you did not clearly establish, as part of an endpoint-specific read-across hypothesis, how the presence of these structural elements among the category members can be linked with the possibility for predicting the properties of the registered substance from data on the category members as required by Annex XI, 1.5. of the REACH Regulation. Further, ECHA notes that no information on the allowed structural differences among the category members is included in the prediction report. According to information provided in the appendix 1 of the report, significant structural differences exist among the analogue substances. The impact of these considerable differences in the chemical structures of the category members on the possibility to predict properties of the registered substance has not been accounted for in the read-across hypothesis.

The prediction report indicates that the prediction has been established for the endpoint *"Prediction of adult and offspring), females), LOAEL, LOAEL (offspring general toxicity), LOAEL systemic, LOAEL(general tox., LOAEL(general toxicity, males), NOAEL, NOAEL (adult general toxicity), NOAE"* . No information on the scope of the investigations and the duration of the source studies conducted with the analogue substances is provided so their relevance for the information expected to be provided to fulfil the information requirement for a screening study on reproductive/developmental toxicity cannot be determined. Therefore, in the absence of robust study summaries presenting the details of the study protocols and demonstrating the validity of these assays, the validity of the prediction cannot be determined.

It remains unclear whether the predicted value of 162 mg/kg/day should be regarded as a LOEL, NOEL or NOAEL for the registered substance. No details on the nature of the recalculations mentioned in the prediction report have been provided. Further, the information included in the report suggests that the data used to establish the prediction has been collected from studies conducted in different species, i.e. rats and mice. No information describing how the potential interspecies differences between rats and mice have been accounted for has been reported.

For all the reasons listed above, ECHA considers that this read-across approach does not allow a reliable prediction of the properties of the registered substance for the endpoint under consideration. As a consequence, ECHA is of the opinion that this information, as currently provided, cannot be regarded as relevant and reliable information in the context of this weight of evidence approach on the dangerous properties of the registered substance.

ECHA considers that the Weight of Evidence approach does not meet the criteria for weight of evidence in accordance to Annex XI, 1.2. This is because even when taken together, the studies do not cover all the parameters of a screening study for reproductive/developmental toxicity. The "one generation" studies have not been performed on the registered substance, and the doses (as described above) do not allow for any conclusions to be drawn on the properties of the registered substance. Furthermore the QSAR study (as described above) does not provide relevant and reliable information in the context of a weight of evidence approach.

Therefore, your adaptation of the information requirement is rejected.

In your comments to the draft decision, you indicated that an OECD guideline 421 study is available, and the dossier will be updated to include this study. Your comments indicate that the study was performed in rats, with the registered substance, at concentrations of 0, 100, 300, and 1000 mg/kg/day, and that as a result of this study, the NOAEL was considered to be 100 mg/kg/day.

ECHA notes that the new study may meet the request in the draft decision. However, as noted in the draft decision sent to you for commenting, 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. All the new information in the later update(s) of the registration dossier will however be assessed for compliance with the REACH requirements in the follow-up evaluation pursuant to Article 42 of the REACH Regulation.

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 methods OECD TG 421 and TG 422, the test is designed for use with rats. On the basis of this default assumption ECHA considers testing should be performed with rats. 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 4.1, October 2015) R.7a, chapter 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.

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

A "pre-natal developmental toxicity study" (test method EU B.31./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 not provided any study record of a pre-natal developmental toxicity study in the dossier that would meet the information requirement of Annex VIII, Section 8.7.1. Instead, in the technical dossier you have provided study records for the following studies:

1) A developmental/reproductive/chronic study (Wernick, 1975), performed on rats (study 1), with no particular guideline cited. The study was not performed on the registered substance, but on a formulation where the concentration of the registered substance is [redacted]% of the formulation. The NOAEL for developmental toxicity for this study has been given as 616 mg/kg/day for the hair dye formulation, which is equivalent to 13.86 mg/kg/day of the registered substance. ECHA notes that this appears to be the same study and same reference used to fulfil the information requirement for the screening study on reproductive/developmental toxicity, discussed above.

2) A developmental/reproductive/chronic study (Wernick, 1975), performed on new Zealand white rabbits (study 2). No particular guideline was cited. Similarly to study 1 above, the test material is a hair dye formulation, where the registered substance represents 2.25% of the formulation. The NOAEL for teratogenicity for this study has been reported as 97.5 mg/kg/bw for the hair dye formulation, which is equivalent to 2.2 mg/kg/bw of the registered substance. ECHA notes that this appears to be the same study and same reference used to fulfil the information requirement for the screening study on reproductive/developmental toxicity, discussed above.

3) A QSAR study that calculates the NOAEL for developmental toxicity of the registered substance at 111 mg/kg/bw.

However, ECHA notes that none of the studies individually is sufficient to fulfil the requirements of a pre-natal developmental toxicity study in a first species for the reasons presented below. Furthermore, ECHA notes that your adaptation does not meet the general rule for adaptation of Annex XI; Section 1.2. (Weight of evidence) for the following reasons:

- **The developmental toxicity studies 1 and 2**

In the first and second studies, the doses of the registered substance are too low to allow for a conclusion on the hazards of the registered substance in this study. Therefore, these two studies on their own are not sufficient to fulfil the information requirement. Furthermore, given the low dose of the registered substance, these studies cannot be considered to be relevant studies in a Weight of Evidence case as the dose doesn't allow for any conclusions on the properties of the registered substance.

- **The QSAR study:**

You have provided information on analogue substances obtained from the OECD QSAR toolbox. As indicated above in section 0 above, ECHA has assessed this line of evidence as a read-across approach. You have attached a prediction report to the endpoint study record.

You listed in the prediction report a series of "referential boundaries" presenting required structural elements for the analogue substances, defined as category members. However ECHA observes that you did not clearly establish, as part of an endpoint-specific read-across hypothesis, how the presence of these structural elements among the category members can be linked with the possibility for predicting the properties of the registered substance from data on the category members as required by Annex XI, 1.5. of the REACH Regulation. Further, ECHA notes that no information on the allowed structural differences among the category members is included in the prediction report. According to information provided in the appendix 1 of the report, significant structural differences exist among the analogue substances. The impact of these considerable differences in the chemical structures of the category members on the possibility to predict properties of the registered substance has not been accounted for in the read-across hypothesis.

The prediction report indicates that the prediction has been established for the endpoint "NOAEL" on the basis of "recalculated endpoint values". No information on the scope of the investigations and the duration of the source studies conducted with the analogue substances is provided so their relevance for the information expected to be provided to fulfil the information requirement for pre-natal developmental toxicity study cannot be determined. No details on the nature of the recalculations mentioned in the prediction report for the different source substances have been provided. Further, the information included in the report suggests that the data used to establish the prediction has been collected from studies conducted in different species, i.e. rats and rabbits. No information describing how the potential interspecies differences between rats and mice have been accounted for has been reported.

For all the reasons listed above, ECHA considers that this read-across approach does not allow a reliable prediction of the properties of the registered substance for the endpoint under consideration. As a consequence, ECHA is of the opinion that this information, as currently provided, cannot be regarded as relevant and reliable information in the context of this weight of evidence approach on the dangerous properties of the registered substance.

ECHA considers that the Weight of Evidence approach does not meet the criteria for weight of evidence in accordance to Annex XI, 1.2. This is because even when taken together, the studies do not cover all the parameters of a pre-natal developmental toxicity study. The "one generation" studies have not been performed on the registered substance, and the doses (as described above) do not allow for any conclusions to be drawn on the properties of the registered substance. Furthermore the QSAR study (as described above) does not provide relevant and reliable information in the context of a weight of evidence approach.

In your comments to the draft decision, you indicated that based on the newly available screening study for reproductive/developmental toxicity (OECD TG 421) which sets a NOAEL of 1000 mg/kg/bw/day, the pre-natal developmental toxicity study does not need to be conducted. As noted in point 4 above, ECHA does not take into account any dossier updates after the draft decision was notified to you.

ECHA points out that a screening study for reproductive/developmental toxicity does not address all the relevant parameters of a pre-natal developmental toxicity study. ECHA considers that such a study is not appropriate to fulfil the information requirement for a pre-natal developmental toxicity study. Nevertheless, ECHA notes that the specific rules for adaptation for Annex IX, Section 8.7 state that "If a substance is known to cause developmental toxicity, meeting the criteria for classification as toxic for reproduction category 1A or 1B: May damage the unborn child (H360D), and the available data are adequate to support a robust risk assessment, then no further testing for developmental toxicity will be necessary."

However, the information provided in your comments indicate that no significant effects were observed and the NOAEL from this study was 1000 mg/kg/bw/day. This information indicates that the study would not meet the specific rule for adaptation quoted above. Therefore ECHA concludes that this study described in your comments would not be appropriate to fulfil the information requirement for a pre-natal developmental toxicity study.

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 EU B.31./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 4.1, October 2015) R.7a, chapter 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.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: EU B.31./OECD TG 414) in a first species (rat or rabbit) by the oral route.

Appendix 2: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation.

The compliance check was initiated on 15 April 2016.

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.

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

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

ECHA received proposal(s) for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendment(s).

ECHA referred the draft decision to the Member State Committee.

You did not provide any comments on the proposed amendment(s).

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-51 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. The substance subject to the present decision is provisionally listed in the Community rolling action plan (CoRAP) for start of substance evaluation in 2018.

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

3. Failure to comply with the request(s) in this decision, or to fulfil otherwise the information requirement(s) with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

4. In relation to the information required by the present decision, the sample of the substance used for the new test(s) 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 test(s) 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 test(s) must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the test(s) to be assessed.

5. In relation to the experimental stud(y/ies) the legal text foresees the sharing of information and costs between Registrant(s) (Article 53 of the REACH Regulation). You are therefore required to make every effort to reach an agreement regarding each experimental study for every endpoint as to who is to carry out the study on behalf of the other Registrant(s) and to inform ECHA accordingly within 90 days from the date of this decision under Article 53(1) of the REACH Regulation. This information should be submitted to ECHA using the following form stating the decision number above at:
https://comments.echa.europa.eu/comments_cms/draftdecisioncomments.aspx?CaseNumber=CCH1_01-2119965131-44-0000

   Further advice can be found at
   http://echa.europa.eu/regulations/reach/registration/data-sharing . If ECHA is not informed of such agreement within 90 days, it will designate one of the Registrants to perform the stud(y/ies) on behalf of all of them.