ECHA
EUROPEAN CHEMICALS AGENCY

Decision number: TPE-D-2114332764-48-01/F Helsinki, 09 June 2016

DECISION ON A TESTING PROPOSAL SET OUT IN A REGISTRATION PURSUANT TO ARTICLE 40(3) OF REGULATION (EC) NO 1907/2006

For SDA Product (desulphurization of exhaust gases by semi-dry absorption method from the coal fired power plants), List No 931-259-6, registration number [redacted]

Addressee: [redacted]

The European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 51 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

I. Procedure

Pursuant to Article 40(1) of the REACH Regulation, ECHA has examined the following testing proposals submitted as part of the registration dossier in accordance with Articles 10(a)(ix) and 12(1)(e) thereof for SDA Product (desulphurization of exhaust gases by semi-dry absorption method from the coal fired power plants), List No 931-259-6, by [redacted] (Registrant):

- Genetic toxicity *in vivo* study (OECD Guideline 474 (Mammalian Erythrocyte Micronucleus Test));
- Developmental toxicity / teratogenicity study (EU Method B.31 (Prenatal Developmental Toxicity Study));
- Long-term toxicity to aquatic invertebrates study (EU Method C.20 (Daphnia magna Reproduction Test)).

This decision is based on the registration dossier as submitted with submission number [redacted], for the tonnage band of 1000 tonnes or more per year.

This decision does not take into account any updates after 2 October 2015, i.e. 30 calendar days after the end of the commenting period.

This decision does not imply that the information provided by the Registrant in his registration dossier is in compliance with the REACH requirements. The decision does not prevent ECHA from initiating a compliance check on the present dossier at a later stage.

ECHA received the registration dossier containing testing proposals for further examination pursuant to Article 40(1) on 10 September 2010. Following a compliance check process to clarify the substance identity the registration was subsequently updated on 30 January 2015 containing the above-mentioned testing proposals.

ECHA held a third party consultation for the testing proposals from 2 September 2011 until 17 October 2011. ECHA received information from third parties (see section III below).

On 27 July 2015 ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision.

On 02 September 2015 ECHA received comments from the Registrant on the draft decision. The ECHA Secretariat considered the Registrant's comments. This has been reflected in Section III (Statement of Reason) of this decision, but Section II (the information required) was not amended.

On 21 January 2016 ECHA notified the Competent Authorities of the Member States of its draft decision and invited them pursuant to Article 51(1) of the REACH Regulation to submit proposals for amendment of the draft decision within 30 days of the receipt of the notification.

Subsequently, proposals for amendment to the draft decision were submitted.

On 26 February 2016 ECHA notified the Registrant of the proposals for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments on the proposals for amendment within 30 days of the receipt of the notification.

The ECHA Secretariat reviewed the proposals for amendment received and amended the draft decision.

On 7 March 2016 ECHA referred the draft decision to the Member State Committee.

By 29 March 2016 the Registrant did not provide any comments on the proposals for amendment.

After discussion in the Member State Committee meeting on 25 – 29 April 2016, a unanimous agreement of the Member State Committee on the draft decision as modified at the meeting was reached on 27 April 2016.

ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

II. Testing required

A. Tests required pursuant to Article 40(3)

The Registrant shall carry out the following proposed tests pursuant to Article 40(3)(a) of the REACH Regulation using the indicated test methods and the registered substance subject to the present decision:

1. Pre-natal developmental toxicity study in rats or rabbits, oral route (Annex IX, 8.7.2.; test method: EU B.31/OECD 414); and
2. Long-term toxicity testing on aquatic invertebrates (Annex IX, 9.1.5.; test method: *Daphnia magna* reproduction test, EU C.20/OECD 211).

The Registrant shall carry out the following additional test pursuant to Article 40(3)(c) of the REACH Regulation using the indicated test method and the registered substance subject to the present decision:

3. Transgenic rodent somatic and germ cell gene mutation assays (Annex IX, Section 8.4., column 2; test method B. 58/OECD 488) in mice or rats treated for 28 days, oral route. The following tissues shall be harvested three days after the cessation of treatment: liver, glandular stomach and germ cells. Mutation frequency shall be assessed in liver and glandular stomach. Germ cells shall be stored for up to 5 years, *or*

In vivo alkaline single-cell gel electrophoresis assay for DNA strand breaks (Comet assay) (Annex IX, Section 8.4., column 2; test method: OECD 489)[1] in rats, oral route, with analysis of DNA damage in the following tissues: liver, glandular stomach and duodenum[2],

while the originally proposed test for a genetic toxicity *in vivo* (OECD Guideline 474 (Mammalian Erythrocyte Micronucleus Test)) proposed to be carried out using the registered substance is rejected pursuant to Article 40(3)(d) of the REACH Regulation.

Note for consideration by the Registrant:

The Registrant 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 to and conforming with the appropriate rules in the respective Annex, and an adequate and reliable documentation.

Failure to comply with the requests in this decision, or to fulfil otherwise the information requirements with a valid and documented adaptation, will result in a notification to the Enforcement Authorities of the Member States.

B. Deadline for submitting the required information

Pursuant to Articles 40(4) and 22 of the REACH Regulation, the Registrant shall submit to ECHA by **17 December 2018** an update of the registration dossier containing the information required by this decision, including, where relevant, an update of the Chemical Safety Report. The timeline has been set to allow for sequential testing as appropriate.

III. Statement of reasons

The decision of ECHA is based on the examination of the testing proposals submitted by the Registrant for the registered substance and scientific information submitted by third parties.

0. Registrants' comments submitted according to Article 50(1) of REACH

The Registrant submitted a comment addressing in a generic way all the information requests addressed in this decision. According to this comment he would like to adapt the requested testing, according to the general rules contained in Annex XI of the REACH Regulation and more specifically proposes to examine the possibility of the use of read-across from meanwhile registered substances which are constituents of the SDA product and if the read-across would not allow a meaningful read-across of all endpoints, the Registrant will consider performing the necessary tests as requested by ECHA.

ECHA notes that the Registrant did not substantiate such an adaptation according to Section 1.5 of Annex XI of REACH with any documentation containing new relevant information of the applied method neither in his comments according to Article 50(1) of REACH nor in a form of a dossier update submitted by the deadline of 2 October 2015 that is mentioned in section I of this decision.

[1] Only the OECD TG is mentioned since it has recently been adopted and the corresponding EU test method has not yet been published.
[2] ECHA considers that the duodenum is the most appropriate part of the intestine to be tested, as it is the first part of the intestine and directly connected to the stomach. The duodenum tissue sampled may contain a small part of the jejunum.

As explained under section II.A of this decision, the Registrant may still adapt the testing requested in this decision 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 to and conforming with the appropriate rules in the respective Annex, and an adequate and reliable documentation. Furthermore, as communicated to the Registrant in the notification letter to the draft decision, any dossier updates after 2 October 2015 will be examined by ECHA only after the deadline which will be set in the final decision has passed.

Therefore ECHA did not amend the information requests of this decision based on the Registrant's comment related to the possible read-across adaptation.

1. Pre-natal developmental toxicity study (Annex IX, Section 8.7.2.)

a) Examination of the testing proposal

Pursuant to Article 40(3)(a) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test.

Pre-natal developmental toxicity studies are part of the standard information requirements as laid down in Annexes IX and X, section 8.7.2. of the REACH Regulation. The information on this endpoint is not available for the registered substance but needs to be present in the technical dossier to meet the information requirements. Consequently there is an information gap and it is necessary to provide information for this endpoint.

The Registrant has submitted a testing proposal for a pre-natal developmental toxicity study according to EU B.31/OECD 414. ECHA considers that the proposed study is appropriate to fulfil the information requirement of Annex IX, Section 8.7.2. of the REACH Regulation.

The Registrant did not specify the species and route to be used for testing. According to the test method EU B.31/OECD 414, the rat is the preferred rodent species, the rabbit the preferred non-rodent species and the test substance is usually administered orally. ECHA considers these default parameters appropriate and testing should be performed by the oral route with the rat as a first species to be used.

b) Consideration of the information received during third party consultation

ECHA received third party information concerning the testing proposal during the third party consultation.

A third party has proposed a strategy for ECHA to consider before further tests on animals are requested. However, third parties were invited, as specified by Article 40(2) of the REACH Regulation to submit "scientifically valid information and studies that address the relevant substance and hazard end-point, addressed by the testing proposal". As the proposal for a strategy as such cannot be regarded information or studies, ECHA concludes that this is not a sufficient basis to fulfil the data/information requirement.

Furthermore, the third party has indicated that due to the irritating/corrosive property of the substance, *in vivo* testing should be prevented based on animal welfare reasons. ECHA notes that under certain conditions *in vivo* testing with corrosive substances is technically possible. As specified in the general part of Annexes VII-X "*in vivo* testing with corrosive substances at concentration/dose levels causing corrosivity shall be avoided".

The test methods for repeated dose toxicity and reproductive toxicity specify that the highest dose level should induce "toxicity but not death or severe suffering". It is the Registrant's responsibility to ensure that appropriate dose/exposure levels are used. Therefore, the information submitted does not provide a sufficient basis on which to reject the proposed test.

c) Outcome

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is requested to carry out the proposed study with the registered substance subject to the present decision: Pre-natal developmental toxicity study in rats or rabbits, oral route (test method: EU B.31/OECD 414).

d) Notes for consideration by the Registrant

In addition, a pre-natal developmental toxicity study on a second species is part of the standard information requirements as laid down in Annex X, Section 8.7.2. for substances registered for 1000 tonnes or more per year (see sentence 2 of introductory paragraph 2 of Annex X).

When considering the need for a testing proposal for a prenatal developmental toxicity study in a second species, the Registrant should take into account the outcome of the pre-natal developmental toxicity study on the first species and all available data to determine if the conditions are met for adaptations according to Annex X, Section 8.7. column 2, or according to Annex XI; for example if the substance meets the criteria for classification as toxic for reproduction Category 1B: May damage the unborn child (H360D), and the available data are adequate to support a robust risk assessment, or alternatively, if Weight of Evidence assessment of all relevant available data provides scientific justification that the study in a second species is not needed. If the Registrant considers that the conditions for adaptations are not fulfilled, he should include in the update of his dossier a testing proposal for a pre-natal developmental toxicity study on a second species. If the Registrant comes to the conclusion that the conditions for these adaptations can be fulfilled, he should update his technical dossier by clearly stating the reasons for proposing to adapt the standard information requirement of Annex X, Section 8.7.2. of the REACH Regulation.

2. Long-term toxicity testing on aquatic invertebrates (Annex IX, 9.1.5.)

Pursuant to Article 40(3)(a) of the REACH Regulation, ECHA may require the Registrant to carry out the proposed test.

"Long-term toxicity testing on aquatic invertebrates" is a standard information requirement as laid down in Annex IX, Section 9.1.5. of the REACH Regulation The information on this endpoint is not available for the registered substance, but needs to be present in the technical dossier to meet the information requirements. Consequently, there is an information gap and it is necessary to provide information for this endpoint.

The Registrant has submitted a testing proposal for testing the registered substance for long-term toxicity testing on aquatic invertebrates *Daphnia magna* reproduction test, EU C.20. ECHA considers that the proposed study is appropriate to fulfil the information requirement of Annex IX, Section 9.1.5 of the REACH Regulation.

According to ECHA *Guidance on information requirements and chemical safety assessment* (version 2.0, November 2014), Chapter R7b (Section R.7.8.5 including Figure R.7.8-4), if based on acute aquatic toxicity data neither fish nor invertebrates are shown to be substantially more sensitive, long-term studies may be required on both. There were no indications in the dossier from the short-term toxicity studies on aquatic species that the fish would be substantially more sensitive than aquatic invertebrates.

In such case, according to the integrated testing strategy, the *Daphnia* study is to be conducted first. If based on the results of the long-term *Daphnia* study and the application of a relevant assessment factor no risks are observed (PEC/PNEC<1), no long-term fish testing may need to be conducted. However, if a risk is indicated, long-term fish testing may need to be conducted.

Therefore, pursuant to Article 40(3)(a) of the REACH Regulation, the Registrant is requested to carry out the proposed study with the registered substance subject to the present decision: Long-term toxicity testing on aquatic invertebrates (Annex IX, 9.1.5.; test method: *Daphnia magna* reproduction test, EU C.20/OECD 211).

Notes for consideration by the Registrant

Once results of the proposed test on long-term toxicity to aquatic invertebrates are available, the Registrant shall revise the chemical safety assessment as necessary according to Annex I of the REACH Regulation. If the revised chemical safety assessment indicates the need to investigate further the effects on aquatic organisms, the Registrant shall submit a testing proposal for a long-term toxicity test on fish in order to fulfil the standard information requirement of Annex IX, 9.1.6. If the Registrant comes to the conclusion that no further investigation of effects on aquatic organisms is required, he shall update his technical dossier by clearly stating the reasons for adapting the standard information requirement of Annex IX, 9.1.6.

3. Transgenic rodent somatic and germ cell gene mutation assays or *In vivo* Mammalian alkaline comet assay (Annex IX, Section 8.4., column 2)

a) Examination of the testing proposal

Pursuant to Article 40(3)(d) and (c) of the REACH Regulation, ECHA may reject a proposed test and require the Registrant to carry out other tests in cases of non-compliance of the testing proposal with Annexes IX, X or XI.

"Mutagenicity" is an information requirement as laid down in Annex VIII, Section 8.4. of the REACH Regulation. Column 2 of Annex IX, Section 8.4. provides that "*if there is a positive result in any of the in vitro genotoxicity studies in Annex VII or VIII and there are no results available from an in vivo study already, an appropriate in vivo somatic cell genotoxicity study shall be proposed by the Registrant*".

The technical dossier contains an *in vitro* study (mammalian cell gene mutation assay on mouse lymphoma L5178Y cells) performed according to EU Method B.17 with the registered substance that shows a positive result without metabolic activation. The positive result indicates that the substance is inducing gene mutations under the conditions of the test.

An appropriate *in vivo* genotoxicity study to follow up the concern on gene mutations is not available for the registered substance but shall be proposed by the Registrant. Consequently, there is an information gap and the Registrant proposed to perform an *in vivo* micronucleus study to generate information for this endpoint.

ECHA notes that the proposed test is not an appropriate test to investigate effects on gene mutations *in vivo* as described in the ECHA Guidance document on information requirements and chemical safety assessment R.7a, chapter R.7.7.1. and figure R.7.7-1 (August 2014). The proposed test is suitable to detect chromosomal aberrations but not gene mutations.

According to the ECHA Guidance on information requirements and chemical safety assessment R.7a, chapter R.7.7.6.3 (August 2014), the transgenic rodent somatic and germ cell gene mutation assays ("TGR assay", OECD 488) and the *in vivo* mammalian alkaline comet assay ("comet assay", OECD 489) are suitable to follow up a positive gene mutation result *in vitro*.

ECHA notes that the TGR assay is usually performed with transgenic mice; the use of transgenic rats should be considered in case the rat is clearly a more appropriate model than the mouse. The comet assay shall be performed in rats because rats are routinely used for this test and also for other toxicity studies.

The Registrant did not specify the route of administration of the *in vivo* genotoxicity testing. ECHA notes that the TGR and comet assay are usually performed with oral dosing. Therefore the test (TGR or comet assay) shall be performed by the oral route.

According to the test method (EU B.58/OECD 488), the TGR assay shall be performed by analysing tissues from liver as slowly proliferating tissue and primary site of xenobiotic metabolism, and from glandular stomach as rapidly proliferating tissue and site of direct contact. Moreover, ECHA notes that according to the OECD 488 the tissues (or tissue homogenates) can be stored under specific conditions and be used for DNA isolation for up to 5 years. Hence, in order to limit additional animal testing, germ cells shall be collected as described in OECD TG 488, and shall be stored for up to 5 years. This duration is sufficient to allow the Registrant or ECHA, in accordance to Annex X, Section 8.4., column 2, to decide on the need for assessment of mutation frequency in the collected germ cells.

According to the test method (OECD 489), the comet assay can be performed by analysing tissues from liver, glandular stomach and duodenum. As set out in the OECD TG 489, the liver is recommended as the primary site of xenobiotic metabolism, and an often highly exposed tissue. The glandular stomach and duodenum are recommended as tissues to examine site of contact effects after oral exposure. In view of several expected or possible variables (different tissue structure and function of the glandular stomach and duodenum; different pH conditions; variable physico-chemical properties and fate of the substance; and probable different absorption rates of the substance and its possible breakdown product(s) between these two tissues), ECHA considers that it is necessary to increase the reliability of the analysis of genotoxicity at the site of contact by sampling both tissues.

b) Consideration of the information received during third party consultation

ECHA received third party information concerning the testing proposal during the third party consultation.

A third party argued that the reason for positive results of the mouse lymphoma assay would be related to cytotoxic and/or high dose levels which would lead to false positive results. ECHA notes that the relative total growth for the highest dose tested in the mouse lymphoma assay was approximately 15%. According to the EU test method B.17 the maximum concentration used for testing should result in approximately 10 – 20% relative total growth, hence the study provided by the Registrant can be seen as acceptable. Hence this would most probably not explain the positive result in the mouse lymphoma assay.

However, it should be noted that the differences in cytotoxicity observed between the mouse lymphoma assay and *in vitro* chromosomal abberation assay (highest concentration tested 2000 ug/ml with no cytotoxicity) may be due to extreme conditions, but this cannot be ruled out with absolute certainty.

The third party also referred to extreme concentrations e.g. osmolality and pH. The pH reported in the study was 11, but there was not reporting on the osmolality in the robust study summary provided in the registration dossier. ECHA notes that extreme osmolar concentrations may results in false positive result, but based on the information provided in the technical dossier ECHA cannot conclude on that.

The Registrant is invited to consider relevance and applicabity of third party comments received fulfilling requirements laid down in Annex IX, 8.4 of the REACH Regulation. ECHA notes that in his formal comments submitted according to Article 50(1) of REACH the Registrant did not provide further information regarding the observations made in the third party comments. Therefore ECHA's above assessment above remains valid and the information provided by the third party does not form a basis to reject the proposed test. ECHA finally notes the adaptation possibilities mentioned under sections II.A and III.0 above and repeats the invitation for the Registrant to consider the relevance and applicabity of third party comments.

c) Outcome

Therefore, pursuant to Article 40(3)(c) of the REACH Regulation, the Registrant is requested to carry out one of the following studies with the registered substance subject to the present decision:

Transgenic rodent somatic and germ cell gene mutation assays (test method: EU B.58/OECD 488) in mice or rats treated for 28 days, oral route. The following tissues shall be harvested three days after the cessation of treatment: liver, glandular stomach and germ cells. Mutation frequency shall be assessed in liver and glandular stomach. Germ cells shall be stored for up to 5 years.

Or

In vivo mammalian alkaline comet assay (test method: OECD 489) in rats, oral route, with analysis of DNA damage in the following tissues: liver, glandular stomach and duodenum,

while the originally proposed test for a genetic toxicity *in vivo* (OECD Guideline 474 (Mammalian Erythrocyte Micronucleus Test)) proposed to be carried out using the registered substance is rejected pursuant to Article 40(3)(d) as non compliant with Annexes VIII and IX of the REACH Regulation.

d) Notes for consideration by the Registrant

The Registrant is reminded that according to Annex X, Section 8.4., column 2 of the REACH Regulation, if positive results from an *in vivo* somatic cell study are available, "the potential for germ cell mutagenicity should be considered on the basis of all available data, including toxicokinetic evidence. If no clear conclusions about germ cell mutagenicity can be made, additional investigations shall be considered".

In case the Registrant decides to perform the TGR assay, he should consider assessing mutation frequency in the collected germ cells in case a positive result is obtained in somatic tissues (i.e. liver or glandular stomach). ECHA invites the Registrant to provide, in the update of the registration dossier submitted by the deadline indicate in section II.B above, a summary of his consideration on the need to perform mutation analysis in germ cells.

In case the Registrant decides to perform the comet assay, he may consider examining gonadal cells, as it would optimise the use of animals. ECHA notes that a positive result in whole gonads is not necessarily reflective of germ cell damage since gonads contain a mixture of somatic and germ cells. However, such positive result would indicate that the substance and/or its metabolite(s) have reached the gonads and caused genotoxic effects. 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.

IV. Adequate identification of the composition of the tested material

The process of examination of testing proposals set out in Article 40 of the REACH Regulation aims at ensuring that the new studies meet real information needs. Within this context, the Registrant's dossier was sufficient to confirm the identity of the substance to the extent necessary for examination of the testing proposal.

In relation to the proposed tests, the sample of substance used for the new studies must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is within the specifications of the substance composition that are given by the joint registrants. It is the responsibility of all joint registrants of the same substance to agree to the tests proposed (as applicable to their tonnage level) and to document the necessary information on their substance composition.

In addition, it is important to ensure that the particular sample of substance tested in the new studies 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 by each registrant. If the registration of the substance by any registrant covers different grades, the sample used for the new studies must be suitable to assess these grades.

V. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Article 51(8) of the REACH Regulation. Such appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on the ECHA's internet page at http://www.echa.europa.eu/regulations/appeals. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

Authorised[2] by Claudio Carlon, Head of Unit, Evaluation, E2

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