Helsinki, 22 March 2019

Addressee: [redacted]

Decision number: CCH-D-2114460631-54-01/F
Substance name: 1,3-diphenylguanidine
EC number: 203-002-1
CAS number: 102-06-7
Registration number: [redacted]
Submission number: [redacted]
Submission date: 07/11/2017
Registered tonnage band: Over 1000

DECISION ON A COMPLIANCE CHECK

Based on Article 41 of Regulation (EC) No 1907/2006 (the REACH Regulation), ECHA requests you to submit information on:

1. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method: OECD TG 443) in rats, oral route with the registered substance specified as follows:**
   - **At least two weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce systemic toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity);**
   - **Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation;**

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 to the REACH Regulation. 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 adequate and reliable documentation.

You have to submit the requested information in an updated registration dossier by **29 July 2021**. You also have to update the chemical safety report, where relevant.

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

The scope of this compliance check decision is limited to the standard information requirement of Annex X, Section 8.7.3. to the REACH Regulation.

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Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals.

Authorised[1] by **Claudio Carlon**, Head of Unit, Hazard Assessment 3

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

Appendix 1: Reasons

1. Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.)

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

The basic test design of an extended one-generation reproductive toxicity study (test method OECD TG 443 with Cohorts 1A and 1B, without extension of Cohort 1B to include a F2 generation, and without Cohorts 2A, 2B and 3) is a standard information requirement as laid down in column 1 of 8.7.3., Annex X. If the conditions described in column 2 of Annex X are met, the study design needs to be expanded to include the extension of Cohort 1B, Cohorts 2A/2B, and/or Cohort 3. Further detailed guidance on study design and triggers is provided in the ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017).

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

a) The information provided

You have not provided any study record of an extended one-generation reproductive toxicity study in the dossier that would meet the information requirement of Annex X, Section 8.7.3.

In the technical dossier you have provided a study record for a "reproduction/developmental toxicity screening test" (test method: OECD TG 421). However, this study does not provide the information required by Annex X, Section 8.7.3. because it does not cover key elements, such as exposure duration, life stages and statistical power of an extended one-generation reproductive toxicity study. More specifically, the main missing key elements are: at least 20 pregnant females per group, and an extensive postnatal evaluation of the F1 generation.

You have also provided several supporting studies such as two sub-chronic studies in rat and mouse ([redacted] 1995), a non-guideline study investigating male sperm morphology and fertility study in mice (Koëter, 1992), two studies of Bempong et al., 1983, which analysed the effects of 1,3-DPG on seminal cytology, testicular development and fertility in mice and hamsters, three other older repeated dose studies (Orlov et al. 1973, Arkhangel'skaya and Roshchina 1963) and a study measuring estrogenic activity by a yeast two-hybrid assay (Ogawa et al. 2006).

ECHA notes that adverse effects on reproductive organs were observed indicating a concern for reproductive toxicity:

- In the rat NTP sub-chronic study ([redacted], 1995) with the registered substance at 250, 500, 750, 1500 and 3000 ppm, females exhibited uterine hypoplasia and a prolonged reproductive cycle in the 750 ppm group (ca. 49 mg/kg b. w. and day) and 1500 ppm-group (ca. 95 mg/kg b. w. and day) in comparison with the controls.

Eventhough the study report refers to the animals' poor condition, at 750 ppm there was only a slight reduction (-6%) in body weight.

From the data presented above it seems that the exposure to the registered substance led to reproductive toxicity effects and it can induce changes in reproductive organs (i.e. uterus and in reproductive cycle). Changes in these parameters may provide indication of endocrine modes of action (Chapter R7a: Endpoint specific guidance Version 6.0.-July 2017).

You have sought to adapt this information requirement with the following justification:

"*In reliable studies, 1,3-diphenylguanidine did not affect the fertility of male mice and male and female rats when administered by gavage up to the maximal tested dose level. In addition to the results of the feeding sub-chronic studies on the rat and mouse, special studies for recognising reproductive toxic effects were also performed. Comparisons of the parameter changes with the results of tests with feed withdrawal infer that the effects observed in the 1,3-diphenylguanidine-treated animals in high concentration groups are a result of the poor general state of health (malnutrition, exhaustion) of the animals and not a direct toxic effect on the reproductive organs. In female rats and mice, foetotoxic, but not teratogenic, effects were seen after the oral administration of maternotoxic doses. DPG is already classified as Repro cat.2 based on not reliable data. Based on the available data (screening study, developmental study in both species), a new study (e.g. OECD 443) will not agravate the classification. Moreover, the DNEL of DPG are based on a NOAEL for which no adverse effects on reproductive organs were observed. A new reproduction study will not change the DNEL and the human health risk assessment. So, in conclusion, a new reproductive study is not needed in this dossier because the study will not have a great additional value*."

While you have not explicitly claimed an adaptation, you have provided information that could be interpreted as an attempt to adapt the information requirement according to Annex XI, Section 1.1. Use of existing data. Hence, ECHA has evaluated your adaptation with respect to this adaptation.

However, ECHA notes that your adaptation does not meet the specific rules for adaptation of general rule for adaptation of Annex XI; Section 1.1. because none of the available data mentioned by you in the adaptation (screening study, developmental study in both species) provide adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test method for this endpoint, i.e. OECD 443. Therefore, your adaptation of the information requirement is rejected.

In your comments on the draft decision you indicated that reprotoxic effects seen in several repeated dose toxicity studies are secondary to systemic toxicity. However, ECHA notes that you did not specify which are these several studies. With reference to the NTP study ([redacted], 1995), as already indicated above, the observed effects were seen in the absence of systemic toxicity.

Furthermore, you stated that the registered substance has already a harmonised classification of Repr. 2 and that "*an EOGRTS will lead to classify* [...] *in the worst case in reprotoxic category 2 but not in category 1B*". Hence, you concluded that the "*EOGRTS is not necessary*".

ECHA notes that as indicated in the ECHA Guidance[2], to fully address fertility, also for classification and labelling purposes, including the categorisation, it is necessary to consider how well all the available parameters address the fertility endpoint. Hence, due to its limitations, a screening study cannot be used to fulfil the information requirement of the EOGRTS. Moreover, the EOGRTS may provide further information for classification and labelling and risk assessment purposes.

Finally in your comments you indicated that the EOGRTS has been requested because of the "*concerns about endocrine activity*" and "*exposure of professionals*". Moreover, you stated that the EOGRTS should not be requested because there are "*existing GLP in vivo animal data [...] addressing the concerns [...] related to endocrine disruption*".

ECHA notes that the EOGRTS at Annex X is not requested on the basis of the concerns related to the potential endocrine mode of action and/or the exposure to professionals. The EOGRTS is requested because it is a standard information requirement at REACH Annex X level.

As explained further below, under the *Extension of Cohort 1B* section, the uses leading to significant exposure to professionals and the indications of modes of action related to endocrine disruption are determinants in setting the study design; that is, the extension of Cohort 1B to include mating of the animals and production of the F2 generation.

With reference to the endocrine disruption screening assays referred to in your comments, as indicated in the ECHA Guidance[3], "*none of the available in vivo assays only focusing on identification of endocrine disrupting potency, such as Uterotrophic assay (EU B.54, OECD TG 440) and Herschberger assay (EU B.55, OECD TG 441), correspond to standard REACH information requirements*". These assays, while they may be "*considered predictive for adverse effects on reproduction, they do not provide adequate information on reproductive toxicity for risk assessment and classification and labelling*". Hence, these endocrine disruption screening assays cannot be used to fulfill the standard information requirement of Annex X, Section 8.7.3.

Hence, 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. Thus, an extended one-generation reproductive toxicity study according Annex X, Section 8.7.3. is required. The following refers to the specifications of this required study.

b) The specifications for the study design

Premating exposure duration and dose-level setting

To ensure that the study design adequately addresses the fertility endpoint, the duration of the premating exposure period and the selection of the highest dose level are key aspects to be considered. According to ECHA Guidance, the starting point for deciding on the length of premating exposure period should be ten weeks to cover the full spermatogenesis and folliculogenesis before the mating, allowing meaningful assessment of the effects on fertility.

[2] ECHA Guidance – Endpoint specific guidance (Chapter R. 7a) - R.7.6.4.2.3, p. 500: https://echa.europa.eu/documents/10162/13632/information_requirements_r7a_en.pdf/e4a2a18f-a2bd-4a04-ac6d-0ea425b2567f
[3] ECHA Guidance – Endpoint specific guidance (Chapter R. 7a) - R.7.6.4.2.9, p. 509: https://echa.europa.eu/documents/10162/13632/information_requirements_r7a_en.pdf/e4a2a18f-a2bd-4a04-ac6d-0ea425b2567f

Ten weeks premating exposure duration is required if there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017). In this specific case, animals of Cohort 1B are mated to produce the F2 generation and, thus, the premating exposure duration will be 10 weeks for these Cohort 1B animals and the fertility parameters will be covered allowing an evaluation of the full spectrum of effects on fertility in these animals. Thus, shorter premating exposure duration for parental (P) animals may be considered.

However, the premating period shall not be shorter than two weeks and must be sufficiently long to reach a steady-state in reproductive organs as advised in the ECHA Guidance. The consideration should take into account whether the findings from P animals after a longer premating exposure duration would provide important information for interpretation of the findings in F1 animals, e.g. when considering the potential developmental origin of such findings as explained in ECHA guidance.

The highest dose level shall aim to induce systemic toxicity, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and systemic toxicity. The dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels.

If there is no relevant data to be used for dose level setting, it is recommended that results from a range-finding study (or range finding studies) are reported with the main study. This will support the justifications of the dose level selections and interpretation of the results.

Extension of Cohort 1B

If the column 2 conditions of 8.7.3., Annex X are met, Cohort 1B must be extended, which means that the F2 generation is produced by mating the Cohort 1B animals. This extension provides information also on the sexual function and fertility of the F1 animals. The extension is inter alia required, if the use of the registered substance is leading to significant exposure of consumers or professionals (column 2, first paragraph, lit. (a) of section 8.7.3., Annex X) and there are indications of one or more relevant modes of action related to endocrine disruption from available *in vivo* studies or non-animal approaches (column 2, first paragraph, lit. (b), third indent of section 8.7.3., Annex X).

Following a Proposal for Amendment from a Member State Competent Authority, ECHA notes that in your comments on the draft decision you provided uses of the registered substance, in formulations for coatings, adhesives, binders and sealants (exemplified by PROCs 10, 11, 13, 23) and uses in lubricants and lubricant additives (PROCs 10, 11, 13, 17) and these were identified as professional uses for at least one co-registration. Hence, the use of the registered substance in the joint submission is leading to significant exposure of professionals.

According to the ECHA Guidance[4], there is significant exposure if *"the substance is intended to be used in the EU by consumers (i.e. members of the public) or professionals, either neat or in a chemical mixture and there is one very wide use or several limited uses potentially affecting many consumers and/or professionals"*. Hence, the uses, as listed in your

[4] ECHA Guidance – Endpoint specific guidance (Chapter R. 7a) - R.7.6-2, p 524-525: https://echa.europa.eu/documents/10162/13632/information_requirements_r7a_en.pdf/e4a2a18f-a2bd-4a04-ac6d-0ea425b2567f

comments on the draft decision, are examples of several uses leading to exposure of professionals. Therefore there is a significant exposure for professionals.

Furthermore, there are indications for endocrine-disrupting modes of action because the registered substance can induce changes in reproductive organs (i.e. uterus).

In your comments on the draft decision you referred to a study program consisting of a set of five *in vitro* and six *in vivo* assays, concluding that "*DPG is unlikely to act as an endocrine disruptor through any of the identified modes of action*." According to the results in the *in vivo* assays the registered substance produced some effects but "*these effects were deemed to be inconsistent with any given mode of action hypothesis*". Based on the conclusions of this evaluation the weight of evidence analysis indicated that the registered substance is "*unlikely to act as an endocrine disruptor*".

ECHA notes that you did not provide the individual study records for these non-animal approaches and specific animal studies, but only a summary of results. Hence, the inconsistency among these assays' results cannot be verified by ECHA as the studies cannot be fully evaluated. ECHA further notes that the provided summary indicates a positive result in the *in vitro* Estrogen Receptor Transcriptional Activation assay, and a slight delay in vaginal opening in the "Pubertal Development and Thyroid Function in Intact Juvenile/Peripubertal Female Rats" test.

As explained above, the repeated dose toxicity (90-day) study with the registered substance ([redacted], 1995) showed effects on the reproductive organs (i.e. uterus), as well as in the length of oestrus cycle, indicating mode(s) of action related to endocrine disruption. Your conclusion that "*DPG is unlikely to act as an endocrine disruptor*" stems from *in vitro* and short-term *in vivo* studies (duration of exposure max 30 days; pubertal male rat study), and therefore they do not invalidate the effects seen in a 90-day repeated dose study.

In view of the above, ECHA concludes that Cohort 1B must be extended to include mating of the animals and production of the F2 generation because the uses of the registered substance are leading to significant exposure of professionals and consumers and there are indications of modes of action related to endocrine disruption from available studies ([redacted], 1995) for the registered substance.

Species and route selection

According to the test method OECD TG 443, the rat is the preferred species. On the basis of this default assumption, ECHA considers that testing should be performed in 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 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a solid, ECHA concludes that testing should be performed by the oral route.

c) Outcome

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: Extended one-generation reproductive toxicity study (test method OECD TG 443), in rats, oral route, according to the following study-design specifications:

- At least two weeks premating exposure duration for the parental (P0) generation;
- Dose level setting shall aim to induce systemic toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity);
- Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation;

While the specifications for the study design are given above, you shall also submit with the new endpoint study record a scientific justification on each of the following aspects: 1) length of the premating exposure duration and dose level selection, 2) reasons for why or why not Cohort 1B was extended, 3) termination time for F2 generation, and 4) reasons for why or why not Cohorts 2A/2B and/or Cohort 3 were included.

Notes for your consideration

No triggers for the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) and Cohort 3 (developmental immunotoxicity) were identified. However, you may expand the study by including Cohorts 2A, 2B and Cohort 3 if new information becomes available after this decision is issued to justify such an inclusion. Inclusion is justified if the available information, together with the new information shows triggers which are described in column 2 of Section 8.7.3., Annex X and further elaborated in ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017). You may also expand the study to address a concern identified during the conduct of the extended one-generation reproduction toxicity study and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the expansion must be documented.

Deadline to submit the requested information in this decision

In the draft decision communicated to you the time indicated to provide the requested information was 24 months from the date of adoption of the decision. In your comments on the draft decision, you requested an extension of the timeline to 36 months. Following a communication from ECHA to provide a justification for the deadline extension request, you submitted a test plan from one test laboratory indicating 13 months waiting time before launching the study and 15 months for conducting the study, i.e. a total of 28 months between the signature of the contract and the final report. Furthermore you indicated that some extra months will be needed to contact other laboratories to compare their availabilities. ECHA notes that the indication of future contacts to other laboratories cannot be taken into consideration. Therefore, ECHA has only partially granted the request and set the deadline to 28 months.

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 27 February 2018.

The decision making followed the procedure of Articles 50 and 51 of the REACH Regulation, as described below:

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

ECHA took into account your comments and did not amend the request however amended 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.

Your comments on the proposed amendment(s) were taken into account by the Member State Committee.

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-63 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

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Appendix 3: Further information, observations and technical guidance

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

2. Failure to comply with the requests in this decision, or to otherwise fulfil the information requirements with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

3. In relation to the information required by the present decision, the sample of the substance used for the new tests must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is suitable to fulfil the information requirement for the range of substance compositions manufactured or imported by the joint registrants.

   It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition. In addition, it is important to ensure that the particular sample of the substance tested in the new tests is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured or imported by each registrant.

   If the registration of the substance by any registrant covers different grades, the sample used for the new tests must be suitable to assess these grades. Finally there must be adequate information on substance identity for the sample tested and the grades registered to enable the relevance of the tests to be assessed.