EUROPEAN CHEMICALS AGENCY

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DECISION ON SUBSTANCE EVALUATION PURSUANT TO ARTICLE 46(1) OF REGULATION (EC) NO 1907/2006

For 1,3-diphenylguanidine, CAS No 102-06-7 (EC No 203-002-1)

Addressees: Registrants of 1,3-diphenylguanidine (concerned registrants)

This decision is addressed to all Registrants of the above substance with active registrations on the date on which the draft for the decision was first sent, with the exception of the cases listed in the following paragraph. A list of all the relevant registration numbers subject to this decision is provided as an annex to this decision.

Registrants meeting the following criteria are *not* addressees of this decision: i) Registrants who exclusively use the above substance as an on-site isolated intermediate and under strictly controlled conditions and ii) Registrants who have ceased manufacture/import of the above substance in accordance with Article 50(3)of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation) before the decision is adopted by ECHA.

Based on an evaluation by French Agency for Food, Environmental and Occupational Health Safety (ANSES) on behalf of the French Competent Authority (evaluating MSCA), the European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 52 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

This decision does not take into account any updates of the registrations of the concerned registrants after 5 September 2013, the date upon which the draft decision was circulated to the other Competent Authorities of the Member States and ECHA pursuant to Article 52(1) of the REACH Regulation.

This decision does not imply that the information provided by the concerned registrants in the registrations is in compliance with the REACH requirements. The decision neither prevents ECHA from initiating compliance checks on the dossiers of the concerned registrants at a later stage, nor does it prevent a new substance evaluation process once the present substance evaluation has been completed.

I. Procedure

Pursuant to Article 45(4) of the REACH Regulation the Competent Authority of France has initiated substance evaluation for 1,3-diphenylguanidine, CAS No 102-06-7 (EC No 203-002-1) submitted by the addressees (concerned registrants) and prepared the present decision in accordance with Article 46(1) of the REACH Regulation.

On the basis of an opinion of the ECHA Member State Committee and due to initial grounds for concern relating to human health/CMR, exposure/high tonnage, risk characterisation ratio>1 (human health) 1,3-diphenylguanidine was included in the Community rolling action plan (CoRAP) for substance evaluation pursuant to Article 44(2) of the REACH Regulation to be evaluated in 2012. The CoRAP was published on the ECHA website on 29 February 2012. The Competent Authority of France was appointed to carry out the evaluation. In the course

of the evaluation, the evaluating MSCA noted additional concerns regarding environmental fate of the substance and composition of the substance.

The evaluating MSCA considered that further information was required to clarify the abovementioned concerns. Therefore, it prepared a draft decision pursuant to Article 46(1) of the REACH Regulation to request further information. It submitted the draft decision to ECHA on 28 February 2013.

Further information requirements related to evaluation of 1,3-diphenylguanidine have been addressed to the relevant registrant in a separate confidential draft decision.

On 4 April 2013 ECHA sent the draft decision to the Registrants and invited them pursuant to Article 50(1) of the REACH Regulation to provide comments within 30 days of the receipt of the draft decision. The Registrants provided comments on the draft decision by the given timeline. Having taken the comments into account, the Competent Authority of France modified Section III of the draft decision.

In accordance with Article 52(1) of the REACH Regulation, on 5 September 2013 the evaluating MSCA notified the Competent Authorities of the other Member States and ECHA of its draft decision and invited them pursuant to Articles 52(2) and 51(2) of the REACH Regulation to submit proposals to amend the draft decision within 30 days.

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

On 11 October 2013 ECHA notified the concerned registrants of the proposals for amendment to the draft decision and invited them pursuant to Articles 52(2) and 51(5) of the REACH Regulation to provide comments on the proposals for amendment within 30 days of the receipt of the notification.

The evaluating MSCA has reviewed the MSCAs' proposals for amendment and amended the draft decision accordingly.

On 21 October 2013 ECHA referred the draft decision to the Member State Committee.

By 11 November 2013 the Registrant provided comments on the proposed amendments and on the draft decision. The Member State Committee took the comments of the Registrant into account. However, the Member State Committee did not consider the Registrant's comments that were not related to the proposals for amendment.

After discussion in the Member State Committee meeting on 10-13 December 2013, a unanimous agreement of the Member State Committee on the draft decision as modified at the meeting was reached on 13 December 2013. ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

II. Information required

Pursuant to Article 46(1) of the REACH Regulation the concerned registrants shall submit the following information using the indicated test methods/instructions and the registered substance subject to the present decision:

1. Further information regarding the composition of 1,3-diphenylguanidine as outlined in section III.1;

2. Quantification of aniline, CAS 62-53-3 (EC No. 200-539-3) produced from 1,3 - diphenylguanidine during each relevant step described in the exposure scenarios

(vulcanisation process, service life of tyres, service life of rubber goods, waste stage and valorisation steps included);

3. Quantification of any by-product produced from 1,3 -diphenylguanidine during each relevant step described in the exposure scenarios (vulcanisation process, life cycle of tyres and rubber goods, waste stage and valorisation steps included);

4. Clarification and detailed justification of the tonnages for each registrant and for each exposure scenario;

5. Add exposure scenarios regarding the valorisation steps of tyres and rubber goods;

6. Tiered approach strategy for the genotoxic potential assessment:

- **Tier 1:**
  Bacterial Reverse Mutation Test (test method EU B.13-14/OECD 471);
- **Tier 2:**
  - **In case of positive or equivocal result of the Bacterial Reverse Mutation Test test: combined *in vivo* Mammalian Erythrocyte Micronucleus test and *in vivo* rat COMET assay by gavage. In combining the two studies and in the absence of an OECD guideline, the Registrant shall follow the EFSA guidance indicating the minimum criteria for the acceptance of in alkaline vivo COMET assay Reports (EFSA 2012) as well as the 3-day treatment schedule described by Bowen et al. (2011); the requested test shall also be in accordance with the test method EU B12 / OECD 474.**
  - **In case of negative result of the Bacterial Reverse Mutation Test test: *in vivo* Mammalian Erythrocyte Micronucleus Test (test method EU B.12/ OECD 474) by gavage;**

7. Toxicokinetics (test method: EU B.36/OECD 417) in case of non conclusive results of the Mammalian Erythrocyte Micronucleus Test;

8. Adsorption – Desorption Using a Batch Equilibrium Method Test (test method: EU C.18/OECD 106);

9. Hydrolysis as a function of pH (test method: EU C.7/OECD 111).

Pursuant to Articles 46(2) of the REACH Regulation, the Registrants shall submit to ECHA by 26 February 2016 an update of the registration dossiers containing the information for the mutagenicity tests required by Section II.6. of this decision. The Registrants shall submit to ECHA by 26 February 2017 an update of the registration dossiers containing the information in points 1,2,3,4,5,7,8 and 9 required by this decision.

At any time, the Registrants shall take into account that there may be an obligation to make every effort to agree on sharing of information and costs with other registrants.

III. Statement of reasons

Based on the evaluation of all relevant information submitted on 1,3-diphenylguanidine and other relevant and available information ECHA concludes that further information is required in order to enable the evaluating MSCA to complete the evaluation of whether the substance constitutes a risk to human health or the environment.

General concern in relation with the initial grounds for concern (human health and exposure)

Based on publications[1,2,3] and reviews[4], it appears that during processes involving high temperature conditions, especially the vulcanisation process, 1,3-diphenylguanidine can form by-products which are substances of concern, such as aniline. No information about these potential by-products is given in the dossier. Several of them could potentially be considered as substances of concern and have to be assessed in order to allow a robust risk characterisation of the substance for the intended uses.

1. Further information regarding the composition of 1,3-diphenylguanidine and, in particular, specifications of the impurities.

The manufacture process of 1,3-diphenylguanidine shows that some substances of concern are probably present in 1,3-diphenylguanidine as impurities. In order to enable a proper assessment of the substance with regard to the CMR and human health initial concerns, the evaluating MSCA needs more information regarding the impurity profile of 1,3-diphenylguanidine (identity, maximum content, origin and potential toxicological relevance, etc.).

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrants are required to provide further information regarding the composition of 1,3 -diphenylguanidine and, in particular, specification of the impurities.

Following Registrants' comments, it must be highlighted that the aim of this requirement is to obtain detailed specifications of 1,3 -diphenylguanidine for each applicant in the respective confidential parts.
For more detailed information, individual confidential requests have been sent to the concerned registrants.
Neither general specification nor general classification should be proposed, several classifications will be proposed if relevant.

Thus the requirement is still valid and the draft decision does not need to be amended.

2. Quantification of aniline, CAS 62-53-3 (EC No. 200-539-3), which is produced from 1,3-diphenylguanidine during each life-cycle stage described in the exposure scenarios (vulcanisation process, service life of tyres, service life of rubber goods, waste stage and valorisation steps included).

As previously mentioned, publications have demonstrated that aniline could be a by-product (degradation product) of 1,3-diphenylguanidine generated during processes using this substance. Aniline CAS 62-53-3 (EC No. 200-539-3) is classified in the Annex VI of CLP (Regulation 1272/2008/CE) as Carc.2 H351; Muta. 2 H341; Acute Tox. 3 H331 and H311 and H301; STOT RE 1 H372; Eye dam 1 H 318, Skin Sens.1 H317; Aquatic Acute 1 H400.

A risk assessment has to be carried out for human health and environment on aniline as a by-product generated during processes using 1,3-diphenylguanidine. In the absence of valid quantitative data in Registrants' dossiers and the literature regarding the quantities of aniline (coming from the transformation of 1,3-diphenylguanidine) generated during processes or remaining in articles, a worst case approach considering that 100% of the used 1,3-diphenylguanidine is transformed in aniline would have to be applied.

[1] Hu, Q., Jin, H.L., Chen, X.A., Wang, S. (2011). Thermal and FTIR spectral studies of N, N'-diphenylguanidine. Journal of Thermal Analysis and Calorimetry. Pages 1-7.
[2] Unterberg, H., Weidenhaupt, H.-J., Wiedemeier, M. (2011). Changes in environmental legislation boost demand for ecologically sound products. Chemicke Listy. Volume 105, Issue 15 SPEC. ISSUE, 2011, Pages s258-s259.
[3] CBI Market Information Database: environmentally sound production: improvement options for the rubber industry.
[4] European union Risk Assessment Report, CAS No 62-53-3, EINECS No 200-539-3, Aniline. Final Report (2004). 1st Priority List, Volume 50.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the registrants are required to carry out estimations on quantity of aniline, CAS 62-53-3 (EC No. 200-539-3) produced from 1,3-diphenylguanidine during each relevant step described in the exposure scenarios (vulcanisation process, service life of tyres, service life of rubber goods) using the registered substance subject to this decision and to update the risk assessment in the registration dossier. A sufficient representativity of the quantification compared to the different exposure scenarii and a sufficient quality regarding the sampling and the analytical techniques will be required to consider the refined figures in the exposure assessment. For further guidance about monitoring, see ECHA guidance R.16 chapter 4: measured data and OECD (2000). Report of the OECD Workshop on Improving the Use of Monitoring Data in the Exposure Assessment of Industrial Chemicals. Organisation for Economic Cooperation and Development (OECD), OECD Environmental Health and Safety Publications, Series on Testing and Assessment No. 18, Paris. For further guidance regarding use of measured data regarding workers' exposure, see ECHA guidance R.14: Occupational exposure estimation, Chapter R.14.4.4 Use of measured data.

Following Registrants' comments, it is acknowledged that the Registrants agree with this requirement.
Thus, the requirement is still valid and the draft decision does not need to be amended.

3. Quantification of any other by-product which is produced from 1,3-diphenylguanidine during each life-cycle stage described in the exposure scenarios (vulcanisation process, life cycle of tyres and rubber goods, waste stage and valorisation steps included).

As previously mentioned, publications have shown that aniline is not the only by-product (degradation product) of 1,3-diphenylguanidine generated during processes using this substance. In order to conduct a proper assessment, these other by-products have to be identified and quantified.

A risk assessment has to be carried out for human health and environment on identified by-products generated during processes using 1,3-diphenylguanidine. In the absence of valid quantitative data in Registrants' dossiers and the literature regarding the quantities of by-products (coming from the transformation of 1,3-diphenylguanidine) generated during processes or remaining in articles, a worst case approach considering that 100% of the used 1,3-diphenylguanidine is transformed in by-products would have to be applied.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrants are required to carry out estimations on quantity of any by-product produced from 1,3-diphenylguanidine during each relevant step described in the exposure scenarios (vulcanisation process, service life of tyres, service life of rubber goods) using the registered substance subject to this decision and to update the risk assessment in the registration dossier. A sufficient representativity of the quantification compared to the different exposure scenarii and a sufficient quality regarding the sampling and the analytical techniques will be required to consider the refined figures in the exposure assessment. For further guidance about monitoring, see ECHA guidance R.16 chapter 4: measured data and OECD (2000). Report of the OECD Workshop on Improving the Use of Monitoring Data in the Exposure Assessment of Industrial Chemicals. Organisation for Economic Cooperation and Development (OECD), OECD Environmental Health and Safety Publications, Series on Testing and Assessment No. 18, Paris.

Following Registrants' comments, the bibliographic data submitted by the Registrants has been taken into account but no clear deduction could be derived regarding the production of tyre and rubber use. Despite this, it is acknowledged that the literature shows no description of nitrosamine generation from 1,3-diphenylguanidine during vulcanization and usually refers to 1,3-diphenylguanidine as a nitrosamine-free vulcanisation agent.

Consequently, the quantification of any other by-product is still valid and the draft decision's justification has been modified accordingly.

Thus, the requirement is still valid and the draft decision does not need to be amended.

Note for consideration by the Registrants:

A quantification of specific identified by-products may be omitted by the registrants to the extent that the Registrants demonstrate that the by-products for which the quantification is omitted do not raise concern.

4. Clarification and detailed justification of the tonnages for each Registrant and for each exposure scenario.

In order to clarify the pattern of uses and to conduct an appropriate combined risk assessment considering the whole tonnage values from the different registrants as requested in section 10 of the CSR, the repartition of the tonnage values must be detailed for each Registrant and for each contributing exposure scenario.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrants are required to give clarifications and a detailed justification of the tonnages for each Registrant and for each exposure scenario and to update the risk assessment in the registration dossier.

Following Registrants' comments, it must be highlighted that the aim of this requirement is to ask each registrant to clarify this information in its confidential part and to clearly attribute a tonnage to each identified use. The evaluating MSCA needs a clear view of the life cycle of 1,3-diphenylguanidine in order to lead a proper assessment of this substance. It is agreed that this must be done in the respect of the free competition rules but the asked clarification does not contradict these rules since this information can be provided separately.

Thus, the requirement is still valid and the draft decision does not need to be amended.

5. Add exposure scenarios for human health and the environment regarding the service life and valorisation steps of tyres and rubber goods. Examination of consumer exposure.

In order to clarify the possible impact on human health or the environment of the service life (e.g. environmental fate of roads' residues of tyres) and the valorisation steps of tyres (landfill of residuals, recovery routes: flooring, shock absorbing mats, paving blocks, artificial turf...[5]) and rubber goods (e.g. potential glove allergy[6] or other articles such as diving suits), additional exposure scenarios are required.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrants are required to add exposure scenarios regarding the service life and the valorisation steps of tyres and rubber goods, to closely evaluate the consumer exposure and to update the risk assessment in the registration dossier.

Following Registrants' comments, it is acknowledged that the Registrants agree with this requirement. It is considered that it is not necessary to consider each article separately which would imply too many data. Only representative scenarios should be provided.

[5] ETRMA website : http://www.etrma.org/tyres/ELTs/recovery-routes-and-trends/material-recovery

[6] Piskin et al., 2006. Glove allergy due to 1,3-diphenylguanidine. Contact Dermatitis, 54: 61-62.

Thus, the requirement is still valid and the draft decision does not need to be amended.

Health concern in relation with the initial ground for concern (CMR)

6. Tiered approach strategy for the genotoxic potential assessment:

- **Initial Draft Decision and general considerations:**

Only the data issued from studies presenting a reliability of 1 or 2 were used for the evaluation by the evaluating MSCA. Other studies provided in the IUCLID dossier were considered as not acceptable for assessment (major methodological deficiencies, insufficient information for assessment). On the basis of these data, no clear conclusion about genotoxicity potential of the registered substance, 1,3-diphenylguanidine, can be made. Thus, a clarification of this endpoint would avoid the use of a worst case for the risk assessment that would consider the substance as genotoxic. This remaining uncertainty would lead to an unacceptable risk and the need for further monitoring studies at the workplace.

The genotoxicity potential of 1,3-diphenylguanidine has been assessed in *in vitro* and *in vivo* assays. Although the results are predominantly negative, some positive or equivocal results were observed in Salmonella typhimurium strains in the presence of induced hamster or rat liver S9 (Mortelmans 1986 & NTP 1995). Moreover, an equivocal result for induction of micronuclei was found in female mice administered 1,3-DPG in dosed feed for 90 days: a significant increase in micronucleated normochromatic erythrocytes was noted in the intermediary dose group (NTP 1995).

This uncertainty regarding the genotoxic potential constitutes a concern as (1) 1,3-diphenylguanidine is chemically related to the aromatic amines which can be nitrosated to potentially mutagenic by-products (2) no information about the carcinogenic potential of 1,3-diphenylguanidine is available and (3) no sufficient information is available on the metabolic pathways of 1,3-diphenylguanidine in mammals. Regarding this last point, liver metabolism predictions performed with the OECD QSAR Toolbox revealed ten possible metabolites for 1,3-diphenylguanidine. Among them, six presented structural alert for genotoxic or were substances with known genotoxic and/or carcinogenic properties (aniline, 4-aminophenol, 2-aminophenol).

- **Registrants' comments on initial Draft Decision:**

Following the Registrants' comments and based on the data on historical controls submitted by the Registrants, these result obtained in the mice micronucleus could be considered within the range of historical control. Nevertheless, it is worth noting that the publication considers that "because the MN studies reported here were conducted by a variety of technicians and scorers over a period of several years, the range of historical control values may not provide a useful basis for judging the result of a single study". In addition, no positive controls were performed during the study to validate the adequacy of experimental conditions.

Consequently, it is considered that the evaluation of all information available is still not sufficient to exclude a genotoxic hazard. This uncertainty is based on:
(1) 1,3 DPG is chemically related to the aromatic amides which can be nitrosated to potentially mutagenic metabolites,
(2) no information about the carcinogenic potential of DPG is available,
(3) no sufficient information is available on the metabolic pathways of DPG in mammals. Regarding this last point, liver metabolism predictions performed with the OECD QSAR Toolbox revealed ten possible metabolites for DPG. Among them, six presented structural

alert for genotoxic (especially for micronucleus) or were substances with known genotoxic and/or carcinogenic properties (aniline, 4 aminophenol, 2 aminophenol) and
(4) The low level of reliability of *in vivo* genotoxicity studies (only one was considered acceptable by the evaluating MSCA) due to some gaps: absence of raw data, positive control, not the more sensitive species tested in the micronucleus test. In addition some positive or equivocal results are observed in the Ames test.

Consequently, no conclusion can be made about the genotoxic potential of 1.3 DPG.

- **Testing required to clarify the concern taking into account PfAs and subsequent Registrants' comments:**

Proposals for Amendment (PfAs) to the draft decision of other MSCAs were received making suggestions on an appropriate strategy to clarify the above concern. In response to these PfAs the Registrants submitted comments suggesting a testing strategy, which ECHA agreed to with the following specifications:

TIER 1: A new Bacterial Reverse Mutation test according to the TG 471 is required in order to cover the concern for gene mutagenicity due to the questionable results observed in NTP study[7]. This test should be performed with and without rodent S9 using a test sample representative of the purity of the current production. The assay with S9 shall be conducted following 2 test conditions: with rat S9 and with hamster S9.

TIER 2:

- In case of a positive or an equivocal result of the Bacterial Reverse Mutation test: the Registrants shall perfom a combined Mammalian Erythrocyte Micronucleus test and *in vivo* rat COMET assay. No OECD guideline currently exists for the comet assay and a combined test, however published protocols are available for performing this test. In this transitional period, the Registrant is advised to follow EFSA guidance indicating the minimum criteria for the acceptance of in alkaline vivo Comet assay Reports (EFSA 2012). Moreover, an adequate treatment schedule for the combined assay (i.e. including a third dose administered on the 3rd day) is described in Bowen et al 2011[Bowen DE, Whitwell JH, Lillford L, Henderson D, Kidd D, Mc Garry S, Pearce G, Beevers C, Kirkland DJ. Evaluation of a multi-endpoint assay in rats, combining the bone-marrow micronucleus test, the Comet assay and the flow-cytometric peripheral blood micronucleus test. Mutation Research 722 (2011) 7–19]. The requested test also has to be in accordance with the test method EU B12 / OECD 474.
- In case of a negative result of the Bacterial Reverse Mutation test: in vivo Mammalian Erythrocyte Micronucleus Test (test method EU B.12/ OECD 474).

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrants are required to carry out the following studies using a tiered approach and using the registered substance subject to this decision:

- Tier 1:
  Bacterial Reverse Mutation Test (test method EU B.13-14/OECD 471);
- Tier 2:
  - In case of positive or equivocal result of the Bacterial Reverse Mutation test: combined *in vivo* Mammalian Erythrocyte Micronucleus test and *in vivo* rat COMET assay by gavage. In combining the two studies and in the absence of an OECD guideline, the Registrant shall follow the EFSA guidance indicating the minimum criteria for the acceptance of in alkaline vivo Comet assay

[7] Mortelmans K, Haworth S, Lawlor T, Speck W, Tainer B, andZeiger E (1986). Salmonella Mutagenicity Tests: II. Results From the Testing of 270 Chemicals. Environ Mutagen, 8, 1-119

Reports (EFSA 2012) as well as the 3-day treatment schedule described by Bowen et al. (2011) and test method EU B12 / OECD 474.

- In case of negative result of the Bacterial Reverse Mutation test: *in vivo* Mammalian Erythrocyte Micronucleus Test (test method EU B.12/ OECD 474) by gavage.

Note for the Registrant:

An additional point needs to be underlined regarding the data gap in the registration dossiers compared with the standard information on reproductive toxicity according to REACH Annex X, Section 8.7.3. Due to the absence of information on the potential for 1,3-diphenylguanidine to have adverse effects on the full range of reproduction endpoints (e.g. fertility, peri- and postnatal effects) it is not currently possible for the evaluating MSCA to make a final conclusion on these endpoints. Despite this, the evaluating MSCA would like to first assess the information regarding mutagenicity obtained as a result of this decision; based on this new information the evaluating MSCA will consider the need for immediate risk management or risk reduction measures. Secondly, at that point of time the evaluating MSCA will (in accordance with REACH Annex X, 8.7. column 2) consider the need to request further information on reproductive toxicity for which there is a data gap in the current 1,3-diphenylguanidine dossier in comparison with the standard information requirements of REACH.

7. Toxicokinetics (Annex VIII, 8.8.1; test method: EU B.36/OECD 417) in case of non conclusive results of the Mammalian Erythrocyte Micronucleus Test

- **Initial Draft Decision and general considerations:**

If the conclusions about mutagenicity remain equivocal, additional investigations about the metabolisation of 1,3-diphenylguanidine in mammals will be needed in order to check whether metabolisation may result in generation of genotoxic metabolites. For such a clarification, it is relevant to investigate the potential formation of genotoxic metabolites *in vivo* and to use a weight of evidence approach using also the results of the further requested mutagenicity studies to conclude on the genotoxic potential of the substance.

Thus, depending on the outcome of the genotoxicity tests required following the tiered approach presented in point 6, the Registrants shall conduct studies examining the toxicokinetics of 1,3-diphenylguanidine through an *in vivo* experiment following the OECD Test guideline 417 (July 2010). In addition, supplemental approaches beyond these experiments may also be necessary: *in vitro* studies using appropriate test sytems (e.g. microsomes and cytosol or S9 fraction from liver) in order to determine potential species differences in biotransformation of DPG between rat, hamster and human.

- **Registrants' comments on initial Draft Decision:**

Following Registrants' comments, it is considered that the genotoxic potential of 1,3-DPG remains equivocal. In absence of clarification of this point; additional investigation about the metabolisation of 1,3-diphenylguanidine in mammals will be needed in order to verify the absence of genotoxic metabolites formation.

In addition, the toxicokinetics data submitted by the Registrant were considered as not sufficient. Indeed, the Iannou and Matthews study did not provide the required information concerning the metabolism pathways of DPG in mammals.

Thus, the requirement is still valid and the draft decision does not need to be amended.

- **Testing required to clarify the concern taking into account PfAs and**

subsequent Registrants' comments:

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrants are required to carry out the following study if considered as necessary as detailed before:
Toxicokinetics (Annex VIII, 8.8.1; test method: EU B.36/OECD 417) using the registered substance subject to this decision.

Notes for consideration by the Registrants:

Taking into account the new data acquired with these previous tests, the risk assessment for 1,3-diphenylguanidine will have to be updated using new DNELs and providing details regarding the recommended RMMs.

Environmental concern raised during evaluation

Assessment of 1,3-diphenylguanidine was based on the available information. Based on these available data, several evaluation reports[8,9] have already pointed out uncertainties in the environmental behavior of this substance, particularly because of (i) its foreseeable very high affinity for organic matter and other matrixes having a high cation exchange capacity; (II) its not readily but inherently biodegradation properties. As a consequence, the following information is required in order to allow a robust risk characterisation of the 1,3-diphenylguanidine for the intended uses.

8. Adsorption – Desorption Using a Batch Equilibrium Method Test (test method: EU C.18/OECD 106).

With a pKa > 10, 1,3-diphenylguanidine is in cationic form at environmentaly relevant pH, and thus has a very high affinity for organic matter and other matrix having a high cation exchange capacity.
According to ECHA guidances[10], the behavior of a substance is based partly on its adsorption / desorption properties. Thus, substances with a Koc below 500 to 1 000 L / kg are generally unlikely adsorbed to sediment. To avoid extensive testing of chemicals, a log Koc (or log Kow) ≥ 3 can be used as a trigger value for sediment effects assessment. In practice a cutoff value for log Kow of 3 can be applied for adsorption potential.
The evaluating MSCA acknowledges that for "classic" organic substances (*i.e.* non polar, non surface active, soluble in water, low adsorptive properties, etc), the Koc should be estimated using read-across or QSAR methods as a first step.

In the information provided by the registrants, the adsorption potential of 1,3-diphenylguanidine is estimated on the basis of log Kow. However for ionised substance at environmentally relevant pH like 1,3-diphenylguanidine, substance adsorption is not triggered by the lipophilicity (*i.e.* log Kow of the substance), but by other mechanisms (*i.e.* ionic interactions). Applying QSAR methods to estimate the adsorption potential of 1,3-diphenylguanidine, would lead to a probable underestimation of Koc, as it has been previously demonstrated for several cationic pesticides[11]. In that report, the estimation of the organic carbon sorption coefficients from the octanol / water partition coefficient of cationic pesticides, based on the QSAR described in the ECHA guideline, induces

[8] Environnement Canada – Health Canada, 2011. Draft screening assessment for the challenge – Guanidine, N,N'-diphenyl-(Diphenylguanidine) – Chemical Abstacts Service Registry Number 102-06-7. http://www.ec.gc.ca/ese-ees/default.asp?lang=En&n=7B3B293F-1
[9] OECD, 2002. SIDS Initial Assessment Report for the 14th SIAM (Paris, 26-28 March 2002). 1,3-Diphenylguanidine, CAS No. 102-06-7. UNEP Publications. http://webnet.oecd.org/hpv/ui/SIDS_Details.aspx?id=9a361ac3-b9ec-48d1-a803-0844b703e8c2
[10] ECHA – Guidance on information requirements and chemical safety assessment – Chapter R.7a : endpoint specific guidance. Version 2.0. November 2012.
[11] Van Beelen, P., 2000. The risk evaluation of difficult substances in USES 2.0 and EUSES – A decision tree for data gap filling of Kow, Koc and BCF. RIVM report 679102050.
http://www.pbl.nl/en/publications/2000/The_risk_evaluation_of_difficult_substances_in_USES_2_0_and_EUSES__A_decision_tree_for_data_gap_filling_of_Kow__Koc_and_BCF

underestimation of the Koc with a factor between 10,000 and 100,000.
Thereby a measured adsorption coefficient is needed for 1,3-diphenylguanidine, in order to have a robust estimation of substance behavior in aquatic and terrestrial compartments. As a consequence, the following test should be performed in order to allow a robust risk characterisation of the 1,3-diphenylguanidine for the intended uses.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrants are required to carry out the following study: Adsorption – Desorption Using a Batch Equilibrium Method Test (test method: EU C.18/OECD 106) using the registered substance subject to this decision.

Following Registrants' comments, the bibliographical reference provided by the Registrants has been considered. ECHA's point of view, supported by Schaffer[12] et al. (2012), is that Franco[13] and Trapp's (2008) regressions still need to be validated for being used for a regulatory purpose. Thereby it is considered that a measured adsorption coefficient is still needed for 1,3-diphenylguanidine, in order to obtain a robust estimation of a key parameter of substance behaviour in aquatic and terrestrial compartments.

Thus, the requirement is still valid and the draft decision does not need to be amended.

9. Hydrolysis as a function of pH (test method: EU C.7/OECD 111).

Wohlfahrt, R. & Niebergall, H. (1984[14] and 1985[15]) investigated the hydrolytic properties of 1,3-diphenylguanidine in relation to the pH value at 80°C. In an acidic environment (pH 3.5) no recognizable hydrolysis of the original substance took place over a period of 500 hours. In the neutral range (pH 7) only 18.1% of 1,3-diphenylguanidine was hydrolyzed after 1000 hours. In the alkaline range (pH 10.5) the half-life was about 168 hours. 1,3-diphenylurea and aniline were identified as hydrolysis products.

No complete relevant information is available on the hydrolytic behaviour under environmentally relevant temperature. Considering the hydrolysis study performed at 80°C and mentionned above, more information is needed regarding the hydrolysis potential of 1,3-diphenylguanidine in environmental conditions. As a consequence, testing its hydrolysis potential as a function of pH should be performed according to test method EU C.7/OECD 111. In case of hydrolysis, we want to highlight that major degradation products should be identified.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrants are required to carry out the following study: Hydrolysis as a function of pH (test method: EU C.7/OECD 111) using the registered substance subject to this decision.

Following Registrants' comments, it is considered that data initially provided by the registrant is supportive information with reliability of 3 mainly because:
- no standard guideline is followed;
- the documentation is insufficient for a robust assessment;

These data should be considered with caution, and more robust information is needed regarding the hydrolysis potential of 1,3-diphenylguanidine in environmental conditions.

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[12] *M. Schaffer, N. Boxberger, H. Börnick, T. Licha, and E. Worch. Sorption influenced transport of ionizable pharmaceuticals onto a natural sandy aquifer sediment at different pH. Chemosphere 87 (5):513-520, 2012.*

[13] *A. Franco and S. Trapp. Estimation of the soil-water partition coefficient normalized organic carbon for ionizable organic chemicals. Environ Toxicol Chem 27 (10):1995-2004, 2008.*

[14] Wohlfahrth, R. & Niebergall, H. (1984). Verhalten von Dicyandiamid, o-Tolylbiguanid und N, N'-Diphenylguanidin in Lebensmitteln. Lebensmittelchem. Gerichtl. Chem., 38: 100-101.

[15] Wohlfahrt, R. & Niebergall, H. (1985). Untersuchung über das Verhalten von Dicyandiamid, o-Tolylbiguanid und N, N'-Diphenylguanidin in Lebensmitteln. Lebensmittelchem. Gerichtl. Chem. 81, 243-250.

Thus, the requirement is still valid and the draft decision does not need to be amended.

Additionnal remark on the identification of degradation products

As previously mentioned, biodegradation data provided in the registration dossiers show that 1,3-diphenylguanidine is not readily biodegradable. Nevertheless, as shown in data presented in the registration dossiers, primary biodegradation can occur, in particular in presence of adapted inoculum. But no data on degradation products is currently available.

According to REACH Regulation, Annex IX, 9.2.3, identification of degradation products should be performed if "*the chemical safety assessment (...) indicates the need to investigate further the degradation of the substance and its degradation products*". According to ECHA guidances, simulation tests are especially useful if it is known from other tests that the tested substance can be degraded. The results of simulation tests may include identification and concentration of major transformation product (> 10%).

It should be quoted that the registrants submitted a testing proposal accepted by ECHA which includes a sediment simulation testing according to test method EU C.24/OECD 308. Test results are currently not available.

Thus the evaluating MSCA highlights that investigation on identification of potential degradation products is expected to be provided by the simulation testing results.

Following Registrants' comments, it should be quoted that registrants submitted a testing proposal accepted by ECHA which include a sediment simulation testing according to test method EU C.24/OECD 308.
As mentioned in endpoint5, new exposure scenarios have been requested regarding the service life and valorisation steps of tyres and rubber goods. The Registrants agreed with this requirement.

As new exposure scenarios are not currently provided by the Registrants, the need for performing sediment simulation testing can not be assessed by the evaluating MSCA.

No modification of the draft decision has been done. Investigation on identification of potential degradation products is still expected to be provided by the simulation testing results.

IV. <u>Adequate identification of the composition of the tested material</u>

The substance identity information submitted in the registration dossiers has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation.

In relation to the required tests, the sample of substance used for the new studies shall have a composition that is within the specifications of the substance composition that are given by all concerned registrants. It is the responsibility of all the concerned registrants to agree on the tested materials to be subjected to the tests subject to this decision and to document the necessary information on composition of the test material. The substance identity information of the registered substance and of the sample tested must enable the evaluating MSCA and ECHA to confirm the relevance of the testing for the substance subject to substance evaluation. Finally, the studies must be shared by the concerned registrants.

V. <u>Avoidance of unnecessary testing by data- and cost- sharing</u>

Avoidance of unnecessary testing and the duplication of tests is a general aim of the REACH Regulation (Article 25). The legal text foresees the sharing of information between

registrants. Since several registrants of the same substance are required to provide the same information, they are obliged to make every effort to reach an agreement for every endpoint as to who is to carry out the test on behalf of the other concerned registrants and to inform ECHA accordingly within 90 days from the date of this decision under Article 53(1) of the REACH Regulation.

If ECHA is not informed of such agreement within 90 days, it shall designate one of the concerned registrants to perform the tests on behalf of all of them. If a registrant performs a test on behalf of other registrants, they shall share the cost of that study equally and the registrant performing the test shall provide each of the others concerned with copies of the full study reports.

This information should be submitted to ECHA using the following form stating the decision number above at:
https://comments.echa.europa.eu/comments_cms/SEDraftDecisionComments.aspxFurther advice can be found at http://echa.europa.eu/datasharing_en.asp.

VI. General requirements regarding Good Laboratory Practice

ECHA always reminds registrants of the requirements of Article 13(4) of the REACH Regulation that ecotoxicological and toxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice (GLP). National authorities monitoring GLP maintain lists of test facilities indicating the relevant areas of expertise of each facility.

VII. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Articles 52(2) and 51(8) of the REACH Regulation. Such an 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.

Jukka Malm
Deputy Executive Director

Annex: List of registration numbers for the addressees of this decision. This annex is confidential and not included in the public version of this decision.