EUROPEAN CHEMICALS AGENCY

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

For Imidazole, CAS No 288-32-4 (EC No 206-019-2)

Addressees: Registrants of Imidazole (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 in the 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 the Health And Safety Executive as the Competent Authority of the United Kingdom (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 1 December 2012.

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 the United Kingdom has initiated substance evaluation for Imidazole, CAS No 288-32-4 (EC No 206-019-2) based on registration dossiers submitted by the 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[1]), its wide dispersive uses and high tonnage, Imidazole 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 29th February 2012. The Competent Authority

[1] CMR = carcinogenic, mutagenic or reprotoxic. In this case the concern was mostly related to the reprotoxicity and mutagenicity endpoints.

of the United Kingdom was appointed to carry out the evaluation. In the course of the evaluation, the evaluating MSCA noted additional concerns regarding environmental hazards. Specifically, further information is needed to allow the assessment of the adequacy and reliability of the available ecotoxicity tests.

The evaluating MSCA considered that further information was required to clarify the above mentioned concerns. Therefore, the evaluating MSCA 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 28th February 2013.

On 4 April 2013 ECHA sent the draft decision to the concerned 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 concerned registrants provided comments to ECHA on the draft decision by the deadline of 6 May 2013.

On 10 May 2013 ECHA notified the evaluating MSCA of the comments received.

The evaluating MSCA considered the comments received from the concerned registrants. The information contained therein was reflected in the Statement of Reasons (section III) and an amendment to the Information Required (Section II) was made.

In accordance with Article 52(1) of the REACH Regulation, on 1 August 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 and ECHA submitted proposals for amendment to the draft decision.

On 6 September 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' and ECHA's proposals for amendment and amended the draft decision accordingly.

On 16 September 2013 ECHA referred the draft decision to the Member State Committee.

On 1 October 2013 the Registrant provided comments on the proposed amendments. The Member State Committee took the comments of the Registrant into account made on the proposals for amendment. However, the member state committe did not consider the Registrants' comments that were not related to the proposal for amendment.

After discussion in the Member State Committee meeting on 4-8 November 2013, a unanimous agreement of the Member State Committee on the draft decision as modified at the meeting was reached on 8 November 2013. ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

Once the information requested by this decision is available in the registration dossiers, the evaluating MSCA will be in a position to reassess the situation and on the basis of that assessment they will decide on the need request further information in order to examine any (remaining) concern for reproductive effects.

II. Information required

Pursuant to Article 46(1) of the REACH Regulation the concerned registrants shall submit the following information on the registered substance in a revised version of their chemical safety report

1. Further detailed information on worker exposure is required for all scenarios to allow an assessment of the adequacy of the risk management measures in place for Imidazole to be made; specifically;

- Descriptive text for each process/task within each scenario;
- Operating conditions to support the selection of individual process category (PROC) coding for each scenario;
- Details of specific tasks within each scenario, (include for each task, - where it takes place, indoor/outdoor, personal protective equipment (PPE) required, respiratory protective equipment (RPE) required, training given);
- All risk management measures (RMMs) used;
- Which modifiers are used within the exposure modelling to take account of RMMs already in place;
- Breakdown of all the input parameters used in the model (e.g. dustiness, low, medium or high);
- Breakdown of any additional modifiers used in the model, e.g. RPE effectiveness, LEV effectiveness;
- Copy of model inputs and outputs;
- Where PPE is specified (e.g. gloves): information on the type of material to be used, and the breakthrough times for the gloves and
- Where RPE is specified: information on the minimum protection factor required for particulate filters and details of maintenance and cleaning procedures.

A generic statement should be provided in the CSRs/dossiers on the need for workers to be trained in the correct use of any control measures, including PPE, that are implemented. Where RPE is recommended, information on the need for wearers to undergo face fit testing should also be included.

The registrants should ensure that any changes made to the exposure assessment as a consequence of the further data requested are carried through and any necessary amendments made to the risk characterisation.

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

2. In vitro mouse lymphoma study (test method EU Method B.17/OECD 476)

Pursuant to Article 46(1) of the REACH Regulation the concerned registrants shall submit revised robust study summaries for the following existing endpoints:

3. Short-term toxicity testing on invertebrates (Daphnia), growth inhibition study aquatic plants (algae), and short-term toxicity testing on fish.

Pursuant to Article 46(1) of the REACH Regulation the concerned registrants with transported intermediate uses shall submit the following detailed information via an update of their dossiers:

4. Documentation giving all relevant details of the strictly controlled conditions in place for all users to support the registrant's claim that Imidazole meets the criteria set out in Article 18 of EC regulation 1907/06.

Pursuant to Article 46(1) of the REACH Regulation the concerned registrants shall submit the detailed information on weight of evidence approach for reproductive toxicity endpoints via an update of their dossiers:

5. Documentation and justification concerning the structurally related substances that the concerned registrants believe would be applicable in an appropriate weight of evidence assessment of the reproductive toxicity effects of Imidazole.

Pursuant to Article 46(2) of the REACH Regulation, the concerned registrants shall submit to ECHA by 21 May 2015 an update of the registration dossiers containing the information required by points 1-5 of this Section II.

III. Statement of reasons

Based on the evaluation of all relevant information submitted on Imidazole and other relevant and available information and taking into account the comments of the concerned registrants, proposals for amendment submitted by Member State Competent Authorities/ECHA and the deliberations of the Member State Committee, 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.

1. Further detailed information on worker exposure

Imidazole was prioritised for substance evaluation to ensure the risk management measures (RMM) currently in place adequately control worker exposure to Imidazole. The registrants of the joint submission have conducted a human exposure assessment in accordance with Article 14 and Annex I of the REACH Regulation and, although they have provided some additional exposure information at the request of the evaluating MSCA, there is currently insufficient detail available in the human exposure assessment to come to a conclusion on the adequacy of the RMM currently in place.

On this basis, the registrants are required to update their CSR to include the information requested in section II (1) for each scenario. This information will increase transparency within the CSR and allow the evaluating MSCA to run Tier 1 models to verify the exposure values put forward by the registrants. More specifically, the information will allow the evaluating MSCA to understand the parameters chosen and used by the registrants within the exposure estimation tools utilised and to determine whether or not appropriate modifiers have been applied. This detail will provide confidence in the exposure estimations presented and allow conclusions to be made regarding the adequacy of the current RMM in controlling workplace exposure to Imidazole.

If as a result of the work already carried out under substance evaluation, the registrants consider there is a need to further revise their CSR and conduct further exposure modelling this should be done using the latest version of the ECETOC TRA (version 3 available from: http://www.ecetoc.org/tra).

Finally, pursuant to Annex VI, section 5 of the REACH Regulation, the registrants are reminded that the information provided in the registration dossier must be consistent with that in the Safety Data Sheet.

In response to ECHA's draft decision, the registrants have submitted comments to the request for further information on worker exposure. The registrants have argued that the descriptions for each PROC code and the additional information in their exposure scenarios should be sufficient to assess the adequacy of their proposed RMMs. The registrants have agreed to modify the way the information is presented in the CSR on receipt of this final decision to provide greater clarity. While the evaluating MSCA considers that the changes to the CSR may resolve some of the requests for information that have been made, this can only be confirmed once the updated CSR is available. In the absence of an updated CSR, the information requirements in this decision, with one exception, have not been modified. The registrants were previously asked to provide any measured exposure data that they hold. Their response indicated that representative exposure data for Imidazole are not available. This request has therefore been removed from this decision.

In response to the registrants' comments on the need for further information regarding personal protective equipment and respiratory protective equipment, the evaluating MSCA refers the registrants to Annex II of the REACH regulation, which states that safety data sheets should make reference to appropriate CEN standards and that detailed specifications of the equipment should be provided. For gloves this should include specific information on the type of glove material, its thickness and given minimum breakthrough times. For completeness, this information should be provided in both the exposure scenarios in the CSR and the safety data sheet. This is consistent with the guidance in ECHA's guidance on Information Requirements and Chemical Safety Assessment (IR and CSA): Chapter 14 occupational exposure estimation (http://echa.europa.eu/documents/10162/13632/information_requirements_r14_en.pdf), which indicates information regarding risk management measures can be included in the CSR.

In response to the registrants' comments, proposals for amendments and the registrants comments on those proposals the evaluating MSCA has amended the request for information on training provision in section II point 1 as follows; to have a generic statement in the CSRs/dossiers of the need for workers to be trained in the correct use of any control measures, including PPE, that are implemented. Where RPE is recommended, the need for wearers to undergo face fit testing should also be included. This is consistent with Chapter R.14.3 of the IR and CSA guidance, which includes a recommendation to provide information on appropriate management systems to ensure that the measures to limit or prevent exposure are correctly applied (e.g. PPE is used correctly). The evaluating MSCA thinks that it is important that training is recognised as a key element of such management systems.

2. *In vitro mouse lymphoma study*

An additional concern for the robustness of the mutagenicity package was identified following a screening of all the available information in the registration dossier of the joint submission. This concern related to Imidazole's potential to cause gene mutations. No concern for clastogenicity or aneugenicity was identified as a robust negative guideline *in*

vivo micronucleus study is available.

The potential for Imidazole to cause gene mutations has been investigated *in vitro* in two Ames tests, one Hypoxanthine-guanine phosphoribosyltransferase (HPRT) study and an *in vitro* unscheduled DNA synthesis (UDS) test. The registrants considered the results of these studies to be negative. Following evaluation, the evaluating MSCA considered the result of the HPRT assay to be equivocal based on isolated increases in mutation frequency above the laboratory's three-fold threshold; in particular an increase observed at the top concentration in one test with S9 (in the absence of significant cytotoxicity). In addition, it was noted the key Ames test was carried out in accordance with OECD TG 471 (1983) and, therefore, doesn't include the fifth strain required by the current OECD TG 471 (1997) guideline. This fifth strain (either *E. coli* WP2 uvrA, or *E. coli* WP2 uvrA (pKM101), or *S. typhimurium* TA102) has the potential to detect certain types of mutagens, such as cross-linking agents or oxidising mutagens, which the other 4 strains may not detect. It is acknowledged that *S. typhimurium* TA102 was investigated in the second Ames study; however, little significance can be attributed to this result as the number of revertants were presented as an average of both initial and repeat experiments (each consisting of three plates) and no information on the variability of the data was available to determine whether this approach was justified. Notwithstanding the negative *in vitro* UDS study, in the absence of *in vivo* gene mutation or carcinogenicity studies, the evaluating MSCA considers there is sufficient residual concern to warrant further investigation to provide reassurance of the lack of mutagenic activity of Imidazole.

This reassurrance could be provided by repeating the HPRT assay and requesting the additional Ames strain be investigated or by requesting the conduct of an *in vivo* gene mutation study. However, the evaluating MSCA believes sufficient reassurance can be gained by the conduct of an *in vitro* mouse lymphoma TK (MLA) assay. This assay is considered more sensitive than the HPRT assay and is of greater relevance to humans than the Ames test as it uses mammalian cells. The evaluating MSCA does not consider there is currently sufficient concern to warrant conduct of an *in vivo* gene mutation study. The need for such a study will be considered once the results of the MLA study are known.

In response to ECHA's draft decision, the registrants provided comments that concerns for this endpoint could be addressed using information generated on structurally related substances. It is acknowledged that this approach may be feasible; however, the registrant has not provided in the technical dossier of the registered substance, a weight of evidence argument or robust study summaries of the studies conducted on the related substances to adequately and reliably address the concern. On this basis, the evaluating MSCA has not modified the information requirements. In addition, the registrants' proposed, should further testing be required, that the Ames and HPRT studies should be repeated. No explanation was provided to explain why this was their preferred approach. In the absence of an appropriate justification and since the MLA is the preferred mammalian gene cell mutation study, the information requirements have not been modified.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the concerned registrants are required to carry out the following study using the registered substance subject to this decision: *In vitro mouse lymphoma study (test method EU Method B.17/OECD 476)*.

3. More detailed information of the available ecotoxicity studies: short-term toxicity on invertebrates (daphnia), growth inhibition study aquatic plants (algae) and short-term toxicity testing on fish.

During the Substance Evaluation, it was noted that the registrants who are part of the joint

submission had provided limited details about the ecotoxicity studies in the registration dossier making it difficult to assess the adequacy and reliability of the information. These data are important to allow accurate evaluation of the potential toxicity to aquatic organisms.

The robust study summaries for the existing endpoints *short-term toxicity testing on invertebrates (Daphnia)*, *growth inhibition study aquatic plants (algae),* and *short-term toxicity testing on fish* should be improved so their validity can be judged; the level of information currently available leads to an unassignable reliability according to the Klimisch criteria. The registrants should refer to the ECHA Guidance Chapter R.7.8.4.1 for a description of the information necessary to judge a study reliable or reliable with restrictions according to the Klimisch criteria. As a minimum, the three robust study summaries should include details on preparation of the test substance stock solution and subsequent test media preparation. For the fish and daphnia acute toxicity study robust study summaries, additions should include details on the number of replicates tested and test temperature during the experiment. Should this additional information not be available, as an alternative the registrants could add results of valid QSAR estimations for the three endpoints to the registration dossier so that each endpoint may be fulfilled in a weight of evidence approach.

In response to ECHA's draft decision, the registrants submitted comments that using data from the analogous substance, 2-methylimidazole, CAS 693-98-1 could give confidence that Imidazole is of low toxicity in fish. The evaluating MSCA agrees that a viable approach could be to consider read-across to an appropriate analogue. This would require a suitable justification to validate the read-across. As no such justification has been presented, the data requirements remain unaltered.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the concerned registrants are required to update their robust study summaries for the endpoints short-term toxicity testing on invertebrates (Daphnia), growth inhibition study aquatic plants (algae), and short-term toxicity testing on fish for the registered substance subject to this decision.

4. Confirmation that the substance, if registered as a transported isolated intermediate, is used under strictly controlled conditions

Imidazole was prioritised for substance evaluation to ensure the risk management measures (RMMs) currently in place adequately control worker exposure to Imidazole. Some registrants have submitted a transported isolated intermediate registration for Imidazole on the basis that the substance is used as an intermediate in accordance with the conditions set out in Article 18(4).

These registrations contain minimal information on the RMMs in place making it difficult to assess whether the substance is really used under strictly controlled conditions, and, consequently that worker exposure to Imidazole is adequately controlled.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the concerned registrants are required to provide the information requested in section II (1) above to allow the evaluating MSCA to conclude 1) on the adequacy of the current RMMs in controlling workplace exposure to Imidazole and 2) that the intermediate is used in accordance with the conditions set out in Article 18 (4). The attention of the registrants is drawn to the ECHA guidance on Chemical Safety Assessment Chapter R.13 Risk Management Measures and Operational Conditions (http://echa.europa.eu/documents/10162/13632/information_requirements_r13_en.pdf)

and ECHA's guidance on intermediates (http://echa.europa.eu/documents/10162/13632/intermediates_en.pdf) for information on the level of detail required.

In response to ECHA's draft decision, information was submitted by a registrant of a transported isolated intermediate registration. This information was deemed sufficient to address the request for this registrant. However, this information request remains in the decision, as there are other registrant(s) who did not provide this information during the commenting period and who did not submit a dossier update containing this information during the time period in which dossier updates were taken into account.

5. Documentation and justification concerning the structurally related substances that the concerned registrants believe would be applicable in an appropriate weight of evidence assessment of the reproductive toxicity effects of Imidazole

ECHA that, the ECHA Committee for Risk Assessment has agreed that Imidazole meets the classification criteria for developmental toxicity Repr Cat 1 B, H360D (May damage the unborn child) pursuant to Regulation (EC) No 1272/2008 (CLP Regulation). However due to the absence of information on the potential for Imidazole 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 ECHA to conclude on these endpoints. Despite this, ECHA would like to first assess the information obtained as a result of this decision; based on this new information ECHA will consider the need for immediate risk management or risk reduction. Secondly, at that point of time ECHA will reconsider the need to request further information on the reproductive toxicity endpoints for which there are data gaps in the current Imidazole dossiers.

In the comments of one of the concerned registrants to the proposal of one Member State to request a two-generation reproductive toxicity study, the registrant explained that the azole class of substances comprise of very different N-heterocyclic substances with different toxicological properties. Moreover, the Registrant informed that lately five closely structurally-related Imidazole derivatives were tested according to OECD test guideline 421 or 422 to screen the fertility and developmental endpoints. The results of these studies would be available and in the view of the registrant the results may address the concerns for reproductive toxicity as indicated in this decision.

With respect to this comment of a concerned registrant it should be noted that as the information referred to by the registrant is not available in the Imidazole dossier ECHA is not in a position to draw any conclusions on the appropriateness and relevance of the comments made by the concerned registrant or the underlying data. Therefore, the concerned registrants are requested to update the Imidazole dossiers with the information that they believe would be applicable in an appropriate weight of evidence assessment of the reproduction effects of Imidazole. This request is without prejudice to the regulatory acceptance of the weight of evidence assessment that can be only decided upon once the data has been made available. In case no clear conclusions can be made, the evaluating MSCA may prepare a draft decision requesting further information to clarify any (remaining) concern on fertility endpoints.

IV. Adequate identification of the composition of the tested material

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 test, the sample of substance used for the new study 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 test 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 study must be shared by the concerned registrants.

V. Avoidance of unnecessary testing by data- and cost- sharing

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.aspx

Further 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.

[redacted]

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.