EUROPEAN CHEMICALS AGENCY

Helsinki, 19 March 2015

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

For 1,4,5,6,7,7-hexachloro-8,9,10-trinorborn-5-ene-2,3-dicarboxylic anhydride, CAS No 115-27-5 (EC No 204-077-3)

Addressees: Registrant(s)[1] of 1,4,5,6,7,7-hexachloro-8,9,10-trinorborn-5-ene-2,3-dicarboxylic anhydride (Registrant(s))

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 for comment, 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 holding active registrations on the day the draft decision was sent are *not* addressees of this decision if they are: i) Registrant(s) who had on that day registered the above substance exclusively as an on-site isolated intermediate under strictly controlled conditions and ii) Registrant(s) 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 Competent Authority of France (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 is based on the registration dossier(s) on 29 April 2014, the day on which the draft decision was notified to the Registrant(s) pursuant to Article 50(1) of the REACH Regulation.

This decision does not imply that the information provided by the Registrant(s) in the registration(s) is in compliance with the REACH requirements. The decision neither prevents ECHA from initiating compliance checks on the dossier(s) of the Registrant(s) 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 1,4,5,6,7,7-hexachloro-8,9,10-trinorborn-5-ene-2,3-dicarboxylic anhydride (also known as chlorendic anhydride), CAS No 115-27-5 (EC No 204-077-3) based on registration(s) submitted by the Registrant(s) and other relevant and

[1] The term Registrant(s) is used throughout the decision, irrespective of the number of Registrants addressed by the decision.

available information 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; suspected sensitizer; Environment/suspected PBT; Exposure/ high worker exposure; high release to the environment, chlorendic anhydride was included in the Community rolling action plan (CoRAP) for substance evaluation to be evaluated in 2013. The updated CoRAP was published on the ECHA website on 20 March 2013. The Competent Authority of France was appointed to carry out the evaluation.

With regard to the concern "suspected sensitizer", the evaluating MSCA considers that this initial concern is sufficiently addressed and concluded that chlorendic anhydride is a possible dermal sensitizing agent in human and that there is sufficient evidence to consider chlorendic anhydride as respiratory sensitizer too. The dermal sensitisation potential of chlorendic anhydride was evaluated in a guinea-pigs maximisation test. Chlorendic anhydride produced a positive response and should be considered as a possible dermal sensitizing agent in humans. Furthermore, the chlorendic anhydride belongs to the cyclic acid anhydrides which can induce irritation and sensitization after direct contact with the skin and the mucous membranes or after exposure by inhalation. Indeed, the cyclic acid anhydrides were widely evaluated and several reported human cases strengthen the evidence on the respiratory sensitization potential[2]. No information is therefore required regarding this endpoint.

With regard to the concern "suspected PBT", the substance should be considered Toxic as it is classified as Carc. 2 and Reprotox. It is likely to be persistent as no biodegradation was observed in the screening test in water. The substance however should not be considered as PBT or vPvB since there is no evidence that bioaccumulation can occur. The log Kow is 1.39 which is well below the screening threshold and there is also evidence of rapid methabolism and excretion in rats. No information is therefore required regarding this endpoint.

The evaluating MSCA considered that further information was required to clarify the following concerns: Human Health/CMR, Environment, Exposure/ high worker exposure. 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 20 March 2014.

On 29 April 2014 ECHA sent the draft decision to the Registrant(s) 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.

Registrant commenting phase

By 5 June 2014 ECHA received comments from the Registrant(s) of which it informed the evaluating MSCA without delay.

The evaluating MSCA considered the comments received from the Registrant(s).
On basis of this information, Section II was amended. An *in vivo* Mammalian Alkaline Comet Assay on the degradation product chlorendic acid (EC n° 204-078-9 and CAS N° 115-28-6) (test method OECD 489) is required (instead of an *in vitro* mammalian cell mutation gene test OECD 476), following a publication provided by the Registrants. The Statement of Reasons (Section III) was changed accordingly.

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[2] Cyclic acid anhydrides: Human health aspects. Concise International Chemical Assessment Document 75. World Health oragnisation.2009

Commenting by other MSCAs and ECHA

In accordance with Article 52(1) of the REACH Regulation, on 30 October 2014 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 of the receipt of the notification.

Subsequently, three Competent Authorities of the Member States and ECHA submitted proposals for amendment to the draft decision.

On 5 December 2014 ECHA notified the Registrant(s) of the proposal[s] 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 those proposals for amendment within 30 days of the receipt of the notification.

The evaluating MSCA reviewed the proposals for amendment received and amended the draft decision.

On 15 December 2014 ECHA referred the draft decision to the Member State Committee.

By 5 January 2015, in accordance to Article 51(5), the Registrant provided comments on the proposals for amendment. In addition, the Registrant provided comments on the draft decision. The Member State Committee took the comments on the proposal(s) for amendment of the Registrant into account. The Member State Committee did not take into account the Registrant's comments on the draft decision as they were not related to the proposal(s) for amendment made and are therefore considered outside the scope of Article 51(5).

After discussion in the Member State Committee meeting on 3-5 February 2015, a unanimous agreement of the Member State Committee on the draft decision as modified at the meeting was reached on 5 February 2015.

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 Registrant(s) shall submit the following information using the indicated test method (in accordance with Article 13 (3) and (4) of the REACH Regulation) and the degradation product 1,4,5,6,7,7,-hexachloro-bicyclo[2,2,1]hept-5-ene- endo cis-2,3-dicarboxylic acid (chlorendic acid) [EC n° 204-078-9 and CAS N° 115-28-6] of the registered substance subject to the present decision:

1. **Vapour pressure determination test at relevant temperature(s) (test method EC A.4 /OECD 104)**

Pursuant to Article 46(1) of the REACH Regulation the Registrant(s) shall submit the following information using the indicated test method (in accordance with Article 13 (3) and (4) of the REACH Regulation) and the degradation product 1,4,5,6,7,7,-hexachloro-bicyclo[2,2,1]hept-5-ene- endo cis-2,3-dicarboxylic acid (also known as chlorendic acid) [EC n° 204-078-9 and CAS N° 115-28-6]of the registered substance subject to the present decision:

2. Adsorption/desorption test using batch equilibrium method (test method EC C.18 /OECD106)

Pursuant to Article 46(1) of the REACH Regulation the Registrant(s) shall submit the following information using the indicated test method (in accordance with Article 13 (3) and (4) of the REACH Regulation) and the registered substance and its impurities potentially of concern subject to the present decision:

3. Short term invertebrates toxicity test (test method EC C.2 /OECD 202)

Pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) shall submit the following information:

4. Information on short-term fish toxicity test

- Based on the results of the short-term toxicity test to invertebrates (OECD 202), where these would show that the toxicity of chlorendic acid and [redacted] is additive, to provide adequate documentation which supports the same approach for toxicity to fish; Or,
- To carry out the following study using the registered substance subject to this decision (containing all the relevant impurities): short term fish toxicity test (test method: EC C.1/OECD 203).

Pursuant to Article 46(1) of the REACH Regulation the Registrant(s) shall submit the following information using the indicated test method (in accordance with Article 13 (3) and (4) of the REACH Regulation) and the registered substance and its impurities potentially of concern subject to the present decision:

5. Activated sludge respiration test (test method EC. C.11/OECD 209)

Pursuant to Article 46(1) of the REACH Regulation the Registrant(s) shall submit the following information using the indicated instructions (in accordance with Article 13 (3) and (4) of the REACH Regulation) and the degradation product 1,4,5,6,7,7,-hexachloro-bicyclo[2,2,1]hept-5-ene- endo cis-2,3-dicarboxylic acid (chlorendic acid) [EC n° 204-078-9 and CAS N° 115-28-6]of the registered substance subject to the present decision:

6. Available data on repeated toxicity, carcinogenicity and reprotoxicity of the degradation product chlorendic acid (EC No 204-078-9 and CAS No 115-28-6)

Pursuant to Article 46(1) of the REACH Regulation the Registrant(s) shall also submit the following information using the indicated test method[s](in accordance with Article 13 (3) and (4) of the REACH Regulation) and the degradation product 1,4,5,6,7,7,-hexachloro-bicyclo[2,2,1]hept-5-ene- endo cis-2,3-dicarboxylic acid (EC n° 204-078-9 and CAS N° 115-28-6) of the registered substance subject to the present decision:

7. Tiered approach strategy for the genotoxic potential assessment on the degradation product chlorendic acid (EC No 204-078-9 and CAS No 115-28-6)

Tier 1:
The in vitro Mammalian Cell Micronucleus Test should be realised first (test method : OECD 487).
Tier 2:
In case of negative result of the in vitro Mammalian Cell Micronucleus Test, an in vitro Mammalian Cell Gene Mutation Test in L5178Y mouse lymphoma cells at TK locus (test method: EU: B.17/ OECD TG 476).
On the basis of the results of the in vitro data requested above, the need to perform additional genotoxicity studies in vivo will be considered.

8. **Derive DN(M)EL which covers the concern of chlorendic acid and revise the DN(M)EL of chlorendic anhydride if necessary.**

9. **Detailed description of the life-cycle with identification of the substance (s) of interest along the whole life-cycle and detailed justifications for each contributing scenarios**

10. **Risk characterisation on human health for chlorendic anhydride and chlorendic acid**

Pursuant to Article 46(2) of the REACH Regulation, the Registrant(s) shall submit to ECHA by **26 September 2016** an update of the registration(s) containing the information required by this decision and, where relevant, an update of the Chemical Safety Report.

III. Statement of reasons

Reasoning 1

The review of all data on chlorendic anhydride and acid (physical-chemical properties, hazards and exposure assessment) demonstrates that the chlorendic acid and chlorendic anhydride are closely related compounds: chlorendic anhydride is rapidly hydrolyzed to chlorendic acid with a half-life of approximately one hour. Conversely when chlorendic acid is heated in an open system, chlorendic anhydride can be formed by deshydratation[3]. The manufacture and the use of chlorendic anhydride can thus lead to the formation of chlorendic acid and human/environmental exposure to both chlorendic anhydre and acid is possible.

1. Vapour pressure determination test at relevant temperature(s) (test method: EC A.4/OECD 104)

In the current available dossier, the Registrants have submitted physico-chemistry parameters mainly for chlorendic anhydride. However, according to the provided dossier, chlorendic anhydride hydrolyses rapidly in chlorendic acid after water contact. Thus, the risk assessment must also be carried out for chlorendic acid. The vapour pressure of the chlorendic acid must be used in exposure assessment calculations but it is not provided in the Registrant's dossier.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required

[3] Chlorendic acid and Anhydride Environmental Health Criteria 185. International Programme on Chemical Safety. 1996

to carry out the following study using the degradation product (chlorendic acid) of the registered substance subject to the present decision: Vapour pressure determination (test method: EU A.4/OECD 104) at all the relevant temperatures (e.g ambient temperature, temperature during process).

2. Adsorption/desorption test using batch equilibrium method (test method: EC C.18 /OECD106)

According to ECHA Guidance[4], 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. In the information provided by the Registrant(s), the adsorption potential of chlorendic anhydride, based on Koc value, is estimated via a QSAR calculation using log Kow.

It has been demonstrated in the dossier that chlorendic anhydride immediately hydrolyses in chlorendic acid after water contact. Then the environmental risk assessment is dealing with this main hydrolysis product. Chlorendic acid has two pKa values below 7 (3.6 and 5.6). These values indicate the substance is under the anionic form at environmentally relevant pH. However, for ionised substances like chlorendic acid, substance adsorption is not triggered by lipophilicity (*i.e.* log Kow of the substance), but by other mechanisms (*i.e.* ionic interactions). Therefore, a QSAR approach is not valid for this substance.
Thereby a measured adsorption coefficient is needed for chlorendic acid in order to have a robust estimation of substance behavior in aquatic and terrestrial compartments. As a consequence, the following test method should be performed in order to allow a robust risk characterisation of the chlorendic anhydride for the intended uses.

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

3. Short-term invertebrates toxicity test (test method: EC C.2/OECD 202)

In the registration dossiers, the available aquatic tests are short-term toxicity test on fish, invertebrates (Daphnia) and algae. Nevertheless, in the robust study summaries of the ecotoxicological test on invertebrates, some deficiencies have been raised by evaluating MSCA, including lack of sufficient information about the occurrence of relevant impurities in the test substance. Indeed, no data is reported on the mortality of control, no analytical monitoring is available and there is not enough information on the derivation of the L(C)D50. Moreover, the substance chlorendic anhydride tested does not contain all the relevant impurities reported in the dossier. One of these impurities is toxic to Daphnia with a NOEC below 1 mg/L according to registration data.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to carry out the following study using the registered substance subject to this decision (containing all the relevant impurities): short-term invertebrates toxicity test (test method: EC C.2/OECD 202).

[4] ECHA – Guidance on information requirements and chemical safety assessment – Chapter R.7a : endpoint specific guidance. Version 2.0. November 2012.

4. Information on short-term fish toxicity

As mention above, in the Registrants' dossiers, the available aquatic tests are short-term toxicity test on fish, invertebrates (Daphnia) and algae. Due to some deficiencies, including lack of sufficient information about the occurrence of relevant impurities in the test substance, the study on fish is considered not reliable. Moreover, the substance chlorendic anhydride tested does not contain all the relevant impurities reported in the dossier. One of these impurities ([redacted]) is toxic to aquatic organisms according to ECHA dissemination website and its maximum amount in the technical chlorendic anhydride could influence the toxicity observed for fish. As this study was carried out in 1977, the chemical manufacture process might have changed, leading to a substance not containing the impurities reported in the registration dossier. Therefore, the data concerning acute toxicity study to fish is not considered as valid.

Therefore, for the reasons outlined in the issue above, the acute toxicity study to fish (REACH registration data) is not considered as valid.

In his comments to the draft decision and proposals for amendment, the Registrant(s) concurred with the conclusion that an assessment of the effect of the presence of [redacted] in the registered substance would give a more comprehensive understanding of the potentional environmental hazards of the substance as supplied. In addition, they concur with the additional option of performing a non-vertebrate animal test, such as the Zebra Fish Embryo Toxicity Test (OECD 236).

However, the Registrant(s) do not agree with the need to conduct the testing stated. In fact, the Registrant(s) is of the opinion that a large body of literature is available for each constituent which concludes that mixtures usually display an additive effect of their individual toxicities. The Registrant(s) suggested that if the OECD 202 (Short-term invertebrate toxicity test) shows that the toxicity of chlorendic acid and [redacted] is additive, it is reasonable to use the available literature data on two constituents to calculate the acute toxicity to fish of the substance as supplied to the market.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to:

- Based on the results of the short-term toxicity test to invertebrates (OECD 202), where these would show that the toxicity of chlorendic acid and [redacted] is additive, to provide adequate documentation which supports the same approach for toxicity to fish; Or,
- To carry out the following study using the registered substance subject to this decision (containing all the relevant impurities): short-term fish toxicity test (test method: EC C.1/OECD 203).

Notes for consideration by the Registrant(s)

Adaptation of this information requirement may be considered by use of Annex XI of REACH, The REACH Endpoint Specific Guidance Document R7b ("pelagic toxicity") and the OECD Series of Testing and Assessment No 171: "Fish toxicity Testing Framework" (2012). When adaptation of the information requirement is made due account should be taken in relation to the content of impurities of the registered substance. Options for adaptation include: use of valid QSAR predictions, read-across to credible structural analogues with valid test data, use of the OECD TG 236 (ZFET test) taking the currently known limitations described in the test guideline adequately into account, and eventually the fish threshold/step down approach (cf. above mentioned OECD Guidance).

5. Activated sludge respiration test (test method EC. C.11/OECD 209)

In the registration dossiers, the available data on micro-organisms come from the ready biodegradation test and are used to calculate the $PNEC_{STEP}$. According to ECHA Guidance R10 (2012), if no standard microbial inhibition test data are available, the $PNEC_{STEP}$ can also be derived from available ready biodegradation tests. An assessment factor of 10 is applied to the test concentration at which no toxicity to the inoculums was observed.

The ready biodegradation test was assessed as reliable by the evaluating evaluating MSCA regarding the ready biodegradation of chlorendic anhydre. However no detail about the impurities of the tested substance is available in the robust study summary. It is not possible to conclude about the toxicity of the substance and its impurities on micro-organisms.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to provide more details about the impurities tested with the declared "pure" substance in the ready biodegradation test. In case no data on the impurities can be submitted, then the Registrant(s) are required to carry out the following study using the registered substance subject to this decision (containing all the relevant impurities): activated sludge respiration test (test method: EC C.11/OECD 209).

For Human Health:

Reasoning 2

In their registration dossiers, the Registrant(s) submitted an assessment of human health hazard and exposure on chlorendic anhydride only.
Based on the above explained *reasoning 1*, it is clear that the toxicity of chlorendic anhydride and chlorendic acid are closely related. Furthermore, in the absence of metabolic pathway on chlorendric anhydride, it is reasonable to consider that, in mammals, chlorendic anhydride will be metabolized to chlorendic acid.

Thus, an assessment of both substances is necessary (Art.46 and 47 of REACH Regulation). No conclusion on any endpoint on chlorendic anhydride could be drawn without the review of the corresponding chlorendic acid endpoint. Consequently, a risk assessment on both substances has to be done. In this context, a reliable hazard assessment to determine the CMR potential (initial concern) and to derive a toxicological reference value (DN(M)EL) and exposure data are needed.

Therefore, the Registrant(s) are required to:

- Fulfill the data gap for the chlorendic acid and produce a reliable hazard assessment through the following toxicological data:
    - Available data on repeated toxicity, carcinogenicity and reproductive toxicity (point 6 below);
    - New genotoxicity studies (point 7 below);
- Then, derive a toxicological reference value - DN(M)EL, which covers the concern of chlorendic acid and revise DN(M)EL for anhydride, if necessary (point 8 below);
- Detail exposure scenarios using the identified relevant form(s) of the substance(s) (point 9 below);
- Finally, characterise the risk for human health for chlorendic anhydride and acid with the newly available information (point 10 below).

6. Available data on repeated toxicity, carcinogenicity and reprotoxicity of the degradation product chlorendic acid.

Based on the above mentioned *reasonings 1* and *2*, toxicological data of the suspected carcinogenic degradation product chlorendic acid are required in order to set a DN(M)EL and to determine the carcinogenic potential for the acid form and also answering to the initial concern "CMR" for the anhydride form. In this context, the following information is necessary, in addition to that found by evaluating MSCA. Good quality data from the literature can also be used:
- repeated toxicity data,
- carcinogenicity data (chlorendic acid is considered as possibly carcinogenic to human (group 2B) by the International Agency for Research on Cancer (IARC) based on sufficient evidence of carcinogenicity (tumors at several different tissue sites) in the two tested rodent species),
- reproduction toxicity data.

Therefore, pursuant to Article 46(1) of the REACH regulation, the Registrant(s) are required to provide available data on repeated toxicity, carcinogenicity and reproduction toxicity of the degradation product chlorendic acid and to perform a human health hazard assessment of this substance.

7. Tiered approach strategy for the genotoxic potential assessment on the degradation product chlorendic acid (EC No 204-078-9 and CAS No 115-28-6):

- **Tier 1:**

The *in vitro* Mammalian Cell Micronucleus Test should be realised first (test method : OECD 487).

- **Tier 2:**

- In case of negative result of the *in vitro* Mammalian Cell Micronucleus Test, an *in vitro* Mammalian Cell Gene Mutation Test in L5178Y mouse lymphoma cells at TK locus (test method: EU: B.17/ OECD TG 476).

On the basis of the results of the *in vitro* data requested above, the evaluating MSCA will consider the need to perform additional genotoxicity studies *in vivo*.

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

Taking into account the fact that an exposure to chlorendic acid was also expected (see mentioned *reasoning 1* and *2* above), the available data regarding the genotoxic potential of chlorendic anhydride and acid were reviewed and are presented below:

Genotoxicity tests	chlorendic anhydride	chlorendic acid
In vitro Ames Bacterial Reverse Mutation Assay	Not mutagenic in the presence and absence of metabolic activation	Not mutagenic in the presence or absence of exogenous metabolism system
In vitro unscheduled DNA Synthesis assay in human WI-38 cells.	Significant increases of the unscheduled DNA synthesis	Not tested
In vitro Mouse lymphoma assay (MLA) L5178Y/TK+/-	Not mutagenic in the presence and absence of metabolic activation	Mutagenic in the absence of S9 activation

Based on these data, ECHA considers that neither clastogenicity nor aneugenicity potential of chlorendic anhydride and acid could be excluded. Indeed, no test assessing the clastogenic and aneugenic potential of both forms is available. Further investigation should

be performed to conclude on this endpoint.

In addition, ECHA considers that the genetic mutation potential of chlorendic anhydride and acid is questionable and cannot be excluded. On one hand, Ames tests gave negative results for both forms. On the other hand, positive results were reported for chlorendic acid in an *in vitro* MLA in the absence of S9; however, these findings are questionable as these were obtained only at the highest cytotoxic concentration. Chlorendic anhydride was not mutagenic in the presence and absence of S9. The positive result of the *in vitro* MLA testing chlorendic acid raises some concerns. However, the poor quality of these test data makes it difficult to conclude. Indeed, the detailed data for the chlorendic acid were not available in the technical dossier, but only the test results. Concerning the chlorendic anhydride the studies were neither performed under GLP nor according to current OECD guidelines; the study summaries on the IUCLID gave too limited information on the conduct of the test and the results are not sufficiently detailed.

Thus, further investigations should be performed to conclude on the genotoxicity endpoint. Since chlorendric anhydride is rapidly hydrolyzed into the acid form (see mentioned *reasoning 1*), the test on the acid form is required and not on anhydride form. However, the results will be extrapolated to the anhydride form.

Therefore, an *in vitro* Mammalian Cell Gene Mutation Test in L5178Y mouse lymphoma cells at TK locus (test method: EU: B.17/ OECD TG 476) and an *in vitro* Mammalian Cell Micronucleus (test method OECD 487) on chlorendic acid (EC n° 204-078-9 and CAS N° 115-28-6) were required in the initial draft decision sent to the Registrant(s).

- **Comments and considerations following the decision-making process:**

Clastogenicity and aneugenicity potential:
The Registrant(s) concur with the conclusion that there is no data available to conclude whether chlorendic acid displays clastogenicity and aneugenicity potential. The Registrant(s) proposed a waiving for this endpoint considering Annex VIII, section 8.4.2 column 2 which states that "*the study does not usually need to be conducted if...the substance is known to be carcinogenic category 1 or 2 or mutagenic category 1, 2 or 3*". Although chlorendic acid does not have a harmonized classification, a self-classification as either Carc. 1B or Carc. 2 is proposed.

ECHA agrees that if the substance is self-classified as Carc. 1A or 1B the proposed waiver referred to Column 2 of Section 8.4.2. of Annex VIII is applicable. However, ECHA notes that even if the substance is self-classified as Carc. 1A or 1B, this does not fully cover for the mutagenicity of the substance. In other words, the fact that the substance is Carc. 1A or 1B does not imply that the substance could not be mutagen. Therefore, as the concern is related to the mutagenicity of the substance in order to determine whether it should be classified for this endpoint and to determine a DMEL or a DNEL considering the carcinogenicity mechanism (with or without threshold), data to conclude on this endpoint could be requested.

Moreover, on the basis of the assessment of the aggregated dossier including new available information, there would be sufficient and conclusive information to request the preparation of an Annex VI dossier (CLH report) concerning carcinogenicity and genotoxicity if needed.

Gene mutation potential:
The Registrant(s) concur with the conclusion that the available data result in discrepancies between the acid and the anhydride. However, according to the Registrant(s) a literature search (*McGregor, D.B.,Brown, A., Cattanach, P., Edwards, I., McBride D., Caspary, W.J.*

(1988). Responses of the L5178Y tk+/tk--- mouse lymphoma cell forward mutation assay, II: 18 coded chemicals. Environ. Mol. Mutagen.; 11(1):91–118) demonstrates that the results of the MLA test on chlorendic acid are suitable for a conclusion on the gene mutation endpoint.

In the light of the data of the publication provided by the Registrant(s) regarding the details of the positive results, ECHA considers that the results are positive only at the highest cytotoxicity concentration. Furthermore, considering that the test is neither performed according to GLP nor according to the OECD guideline and the test substance is an acid, ECHA questions whether the positive results reflect genotoxic effects or the secondary effects due to the assay conditions.

This issue was presented at the Member State Committee and comments were raised on the findings of the study. The conclusions are that the data on the *in vitro* Mouse Lymphoma Assay were not robust enough to justify a follow-up study *in vivo* at this point in time. The Member State Committee concluded on the need to perform the *in vitro* Mammalian Cell Gene Mutation Test in L5178Y mouse lymphoma cells at TK locus (test method: EU: B.17/ OECD TG 476) according to GLP and OECD guideline.
The new strategy lead to a change in the deadline specified in Section II from 24 to 18 months taking into account the time needed to perform the tests.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to carry out the following studies using a tiered approach and using the degradation product chlorendic acid (EC No 204-078-9 and CAS No 115-28-6):

- Tier 1:

The *in vitro* Mammalian Cell Micronucleus Test should be performed first (test method : OECD 487).

- Tier 2:

- In case of negative result of the *in vitro* Mammalian Cell Micronucleus Test, an *in vitro* Mammalian Cell Gene Mutation Test in L5178Y mouse lymphoma cells at TK locus (test method: EU: B.17/ OECD TG 476) is to be performed. On the basis of the results of the *in vitro* data requested above, the evaluating MSCA will consider the need to perform additional genotoxicity studies *in vivo.*

8. Derive the toxicological reference value – DN(M)EL - which covers the concern of chlorendic acid and revise the DN(M)EL of chlorendic anhydride if necessary.

In the dossier under evaluation, the Registrant(s) submitted an assessment of human health hazard and exposure on chlorendic anhydride only. Based on the above mentioned *reasonings 1* and *2* and on the data required in the requirements 6 and 7, a DNEL or DMEL for chlorendic acid, considering the carcinogenicity mechanism (with or without threshold) has to be determined by the Registrant(s). This DN(M)EL should be determined following the procedure laid out in the REACH Guidance on information requirement and Chemical Safety Assessment.

If necessary, based on the results of the requested studies on genotoxicity, the DN(M)EL of chlorendic anhydride should be revised.

Taking into account the submitted data on the acid the appropriate DN(M)EL of acid should be used for each exposure suitable scenario.

Note for the Registrant(s):

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 IX, Section 8.7.3. Due to the absence of information on the potential for chlorendic anhydride to have adverse effects on the full range of reproduction endpoints (e.g. fertility), 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 IX, 8.7. column 2) consider the need to request further information on reproductive toxicity for which there is a data gap in the current chlorendic anhydride dossier in comparison with the standard information requirements of REACH.

9. Detailed description of the life-cycle with identification of the substance(s) of interest along the whole life-cycle and detailed justifications for each contributing scenarios

Due to a high exposure of workers and high releases to the environment, concerns have been identified for the anhydride and acid forms of the substance.

In order to lead a proper risk assessment, the exposure scenarios have to cover the whole life-cycle of the substance (from the chemical production to the service-life of treated articles) for each uses of the substance (manufacture of chemicals, plastics, etc.) and/or each treated matrix (plastics, resins, polymers, etc). Some missing scenarios have been identified and no justification is provided. Moreover, the provided information does not allow a correct identification of the relevant substance(s) of interest along the different steps of the life cycle of chlorendic anhydride: i.e., chlorendic anhydride, chlorendic acid, impurities and post-reacted new chemical products.

In order to clarify the exposure and the emission pathways, more information on the life cycle of the substance is needed. For each step of the life cycle, an exposure scenario must be proposed, detailed and justified using the identified relevant form(s) of the substance(s).

The Registrant(s) is reminded that the exposure scenarios have to be extensively and properly described and all considered parameters or deviation from default parameters have to be explained and justified in accordance with REACH guidance documents. Furthermore, a brief description of the sequence of the activities/tasks at the industrial sites is also required to enable a better understanding of the practices. Especially regarding environmental assessment, the data provided in the current registration dossier are not properly justified in case of deviations from default parameters. Therefore, in order to clarify the exposure assessment calculations and to allow the evaluating MSCA to evaluate the appropriateness of the descritptions and calculations, a more detailed description of the plant site(s), the used tonnage at each step of the life cycle, the processes, the release factors and the risk management measures with their efficiency is required. All the parameters have to be explained and justified based on the guidance document values used for this risk assessment.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) are required to provide the following information: detailed description of the life cycle with identification of the substance(s) of interest along the whole life-cycle and detailed justifications for all the parameters used for the exposure assessment.

10. Risk characterisation on human health for chlorendic anhydride and chlorendic acid.

Based on requirements 6 to 8, a new global risk characterisation should be performed considering chlorendic acid and anhydride.

IV. Adequate identification of the composition of the tested material

In relation to the required experimental stud(y/ies), the sample of the substance to be used shall have a composition that is within the specifications of the substance composition that are given by all Registrant(s). It is the responsibility of all the Registrant(s) to agree on the tested material to be subjected to the test(s) 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 test(s) must be shared by the Registrant(s).

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

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

Further advice can be found at http://echa.europa.eu/datasharing_en.asp.

If ECHA is not informed of such agreement within 90 days, it will designate one of the Registrant(s) to perform the stud(y/ies) on behalf of all of them.

VI. 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]
Leena Ylä-Mononen
Director of Evaluation