Helsinki, 28 May 2019

Addressee: [redacted]

Decision number: CCH-D-2114471542-50-01/F
Substance name: Octene, hydroformylation products, low-boiling
EC number: 273-110-1
CAS number: 68938-03-4
Registration number: [redacted]
Submission number: [redacted]
Submission date: 22/10/2018
Registered tonnage band: Over 1000

DECISION ON A COMPLIANCE CHECK

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

1. **Extended one-generation reproductive toxicity study (Annex X, Section 8.7.3.; test method OECD TG 443) in rats, oral route with the registered substance specified as follows:**
   - **Ten weeks premating exposure duration for the parental (P0) generation;**
   - **Dose level setting shall aim to induce systemic toxicity at the highest dose level;**
   - **Cohort 1A (Reproductive toxicity);**
   - **Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation; and**
   - **Cohorts 2A and 2B (Developmental neurotoxicity).**

You have to submit the requested information in an updated registration dossier by ***04 June 2021***. You shall also update the chemical safety report, where relevant.

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

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

Appeal

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

Authorised[1] by Ofelia Bercaru, Head of Unit, Hazard Assessment.

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

Appendix 1: Reasons

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

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

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

In Decision CCH-D-2114360325-54-01/F ECHA concluded, after evaluating the relevant information in your registration dossier, that an extended one-generation reproductive toxicity study according Annex X, Section 8.7.3. is required. In that decision it was indicated that the information provided on this endpoint for the registered substance in the technical dossier does not meet the information requirement. Consequently there is an information gap and it is necessary to provide information for this endpoint.

In that same decision ECHA requested a sub-chronic toxicity study (90-day). The decision indicated that the sub-chronic toxicity study shall be conducted before the extended one-generation reproductive toxicity study and the results from the 90-day study shall be used, among other relevant information, to decide on the study design of the extended one-generation reproductive toxicity study.

In accordance with that decision you have provided the results of a sub-chronic toxicity study (90-day). In light of these results, you also provided your considerations of the design of the extended one-generation reproductive toxicity study, proposing "*extended one-generation reproductive toxicity - with F2 generation (Cohorts 1A, and 1B with extension)*".

Based on the experimental results submitted for the sub-chronic toxicity study (90-day), ECHA and the Member State authorities have re-evaluated the design of the extended one-generation reproductive toxicity study.

One Member State authority considered that there was a need to include Cohorts 2A and 2B in particular based on the following findings:

- "*abnormal pink colouration of the sciatic nerve and peripheral nerves*" (OECD TG 422),
- behavioural effects (OECD TG 408): "*Slight statistically significant decreases were observed at functional tests: landing foot splay in mid- and high dose males and grip strength in high dose males, at the end of treatment; landing foot splay and motor activity in high dose males after 4 weeks of recovery.*"

This Member State authority also considered that Cohort 3 should be included in particular based on the following findings:

- "*effects observed on the spleen weight in males*" (OECD TG 408),
- change in blood parameters (OECD TG 408).

As a Member State authority considered that the study design of the extended one-generation reproductive toxicity study needs to be revised a new decision making process under Articles 50 and 51 of the REACH Regulation has to be followed for this information requirement.

Following proposals for amendment (PfAs) submitted by some Member State Competent Authorities (MSCAs) ECHA has agreed to request the inclusion of Cohorts 2A and 2B (developmental neurotoxicity) as specified below.

The specifications for the study design

Premating exposure duration and dose-level setting

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

Ten weeks premating exposure duration is required if there is no substance specific information in the dossier supporting shorter premating exposure duration as advised in the ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017). In this specific case ten weeks exposure duration is supported by the lipophilicity of the substance (log Kow 5.4-6.2) to ensure that the steady state in parental animals has been reached before mating.

According to the initial considerations provided in submission TW490214-02, you intend to set the dose levels based on the available OECD TG 422, 408 and 414 studies.

ECHA considers that such approach is acceptable as long as it is shown that the dose level you have set induces systemic toxicity at the highest dose level, but not death or severe suffering of the animals, to allow comparison of reproductive toxicity and systemic toxicity. Furthermore, the dose level selection should be based upon the fertility effects with the other cohorts being tested at the same dose levels.

If you decide to conduct a separate range-finding study (or range finding studies) to help in the dose level selection, it is recommended that its results are reported with the main study. This will support the justifications of the dose level selections and interpretation of the results.

Extension of Cohort 1B

If the column 2 conditions set out in part (a) and one of the bullet points in part (b) of section 8.7.3., Annex X are met, Cohort 1B must be extended, which means that the F2

generation is produced by mating the Cohort 1B animals. This extension provides information also on the sexual function and fertility of the F1 animals.

The use of the registered substance is leading to significant exposure of consumers and professionals because the registered substance is used by consumers and professionals as fuels (PROC 16).

One of the MSCAs submitted a proposal for amendment (PfA) to request ECHA to include additional information to demonstrate that the substance has uses leading to significant exposure of consumers or professionals; "*e.g. on tonnage of this particular use and an indication of the number of consumers/professionals involved*". According to the MSCA, if the significant exposure cannot be sufficiently justified then the extension of Cohort 1B should not be requested.

In your comments on the PfA you indicated that the use in fuels is leading to limited exposure to consumers and professionals. Additionally, you stated that the registered substance represents a maximum of 0.1% of the fuel market and when used in fuel the maximum concentration of the registered substance is [redacted]. You also refer to the efficiency of the Stage II petrol recovery system, where according to the EU Directive 2009/126/EC, it should be equal or greater than 85%. Based on the limited exposure levels you concluded that the exposure is considered not to be significant.
With reference to the MSCAs request to provide additional information ("*tonnage of this particular use*" and "*indication of the number of consumers/professionals involved*") and also to your comments (actual exposure levels of the registered substance), ECHA considers that the condition of Annex X, column 2, Section 8.7.3. (a) only requires identified "*uses leading to significant exposure of consumers or professionals*".

According to the ECHA Guidance Chapter R.7a, uses are leading to significant exposure "*if the substance is intended to be used in the EU by consumers (i.e. members of the public) or professionals, either neat or in a chemical mixture and there is one very wide use or several limited uses potentially affecting many consumers and/or professionals, then this is considered as meeting the criterion*"[2].

ECHA notes that this substance, which is registered at the highest tonnage band (above 1000 tpa), is mainly supplied as a fuel additive (PROC 16). Under PROC 16 (PC 13) it is used by professional workers for refueling and maintenance of combustion engines, and by consumers for the refueling of cars. Moreover, the environmental release category (ERC) identified in the current dossier, is ERC8e; that is widespread use of reactive processing aid (no inclusion into or onto article, outdoor). ECHA notes that this use descriptor applies to uses by the public at large or by professional workers[3].

In view of the above, ECHA considers that the requirement of significant exposure is fulfilled.

In your comments to the PfA you also provide a general comment concerning the "*little or no impact*" of the second generation findings to the "*overall hazard and risk assessment*". ECHA notes that the extension to mate Cohort 1B animals to produce the F2 generation is an adaptation to the EOGRTS standard information requirement, and must be conducted if

[2] Guidance on Information Requirements and Chemical Safety Assessment Chapter R.7a: Endpoint specific guidance, page 525.
[3] Guidance on Information Requirements and Chemical Safety Assessment Chapter R.12: Use description, page 61.

the conditions for triggering, according to Annex X, column 2, Section 8.7.3., are met.

You also expressed your intention to update the exposure assessment of the registration dossier. ECHA notes that the evaluation of all the new information provided in the later update(s) of the registration dossier will only be performed at the follow-up evaluation stage, pursuant to Article 42 of the REACH Regulation (after the final decision is sent out by ECHA).

Therefore, as explained above, the condition set out in part (a) of the second column of Section 8.7.3, Annex X has been met.
Furthermore, there are indications that the internal dose for the registered substance will reach a steady state in the test animals only after an extended exposure because the partition coefficient log K_{ow} for the registered substance is 5.4-6.2 (at 26°C). In your considerations for the study design (submission [redacted]), you also refer to this condition. Indeed, according to ECHA's Guidance on Information Requirements and Chemical Safety Assessment Chapter R7a (p. 526): "An octanol-water partition coefficient (log Kow) value (e.g. above 4.5) indicates (bio)accumulative potential... ". Accordingly, the condition set out in the second bullet point of part (b) of the second column of Section 8.7.3, Annex X has been met.

Therefore, ECHA concludes that Cohort 1B must be extended to include mating of the animals and production of the F2 generation.

Cohorts 2A and 2B

The developmental neurotoxicity Cohorts 2A and 2B need to be conducted in case of a particular concern on (developmental) neurotoxicity as described in column 2 of section 8.7.3., Annex X. When there are triggers for developmental neurotoxicity, both the Cohorts 2A and 2B are to be conducted as they provide complementary information.

A number of PfAs explain that the conditions for triggering cohorts 2A and 2B have been met.

In light of the considerations set out in the PfAs, ECHA notes that existing information on the registered substance derived from the available *in vivo* repeated dose toxicity (90-day) study shows evidence of adverse effects on the adult nervous system. Specifically:

(1) The 90-day study showed a dose-related reduction in the sensory reactivity (-18% at top dose, statistically significant) in males, and sensory reactivity remained at a lower level after 4 weeks recovery albeit not statistically significantly different from control.

(2) The 90-day study also showed a dose-related decrease in absolute brain weight (5.7% lower compared to the control values at top dose; statistically significant). Brain weight is commonly considered least prone to weight changes as secondary effect to body weight increase or decrease (Michael et al., 2007[4]; Nirogi et al., 2014[5]) and hence it is questionable that a 7% body-weight decrease can cause a statistically significant reduced absolute brain

[4] Michael B., Yano B., Sellers R.S., Perry R., Morton D., Roome N., Johnson J.K., and Schafer K. (2007): Evaluation of organ weights for rodent and non-rodent toxicity studies: A review of regulatory guidelines and a survey of current practices. Toxicologic Pathology 35 (5), 742-750. DOI: 10.1080/01926230701595292
[5] Nirogi R., Goyal V.K., Jana S., Pandey S.K., and Gothi A. (2014): What suits best for organ weight analysis: Review of relationship between organ weight and body / brain weight for rodent toxicity studies. International Journal Of Pharmaceutical Sciences And Research 5 (4), 1525-1532. DOI: 10.13040/IJPSR.0975-8232.5(4).1525-32

weight. Additionally, the reduction in brain weight is dose-dependent, indicating a treatment-related effect.

(3) As supporting evidence, you report a statistically-significant decrease in grip strength in high dose males (without providing quantification) at the end of treatment.

(4) In the 90-day study, and after the recovery period only, the high dose males show a 66% decrease in motor activity, which is statistically significant.

ECHA also notes that these four effects of the substance are plausibly linked through a neurotoxic mechanism of action- the concordance of findings in several tests increases the concern. Hence, ECHA considers that these functional adverse findings indicate a particular concern for developmental neurotoxicity (DNT).

In your comments on the PfAs, you address the above points, which together justify the particular concern for developmental neurotoxicity, as follows:

(1) You state there is no such effect in the OECD 422 study and you do not address the dose-related reduction in the sensory reactivity (-18% at top dose, statistically significant) in males in the 90-day study.

In view of the lower exposure time for males in the OECD 422 study as compared to the 90-day study, the lack of effect seen in the OECD 422 study does not remove the concern from the results in the 90-day study.

(2) You argue that the decrease in brain weight is correlated with reduced body weight gain and so brain weight is related to the general condition of the animals. You also argue that the lack of clinical signs/ behaviour changes and histopathology allows you to conclude that the effect on brain is not treatment related.

Your unsupported assertions on the relationship between brain weight and body weight do not outweigh the concerns set out in (2) above. Further, ECHA considers that there are multiple functional and behavioural findings, also described above, which add concern to the findings on brain weight, and so it is not possible to conclude that the brain weight effect is not treatment related. ECHA notes that there is an inconsistency between your arguments that (a) the decrease in brain weight is caused by the substance reducing body weight gain and (b) the effect on brain is not treatment related.
(3) You argue that the decrease in grip strength is a function of reduced body weight. Further you cite Maurissen (Neurotoxicology and Teratology, Volume 25, 2003, Pages 543-553.) which shows that dietary restriction can reduce grip strength. You also note the lack of effect on grip strength in the OECD 422 study.

Firstly, ECHA notes that you failed to make the referred data available in the robust study summary in the dossier. Secondly, ECHA notes that Maurissen shows that a large decrease in body weight from dietary restriction (26% lower than controls) leads to a more modest decrease in forelimb grip strength (18%). By contrast, according to your comment, the substance causes a 7% decrease in body weight (compared to control) but a much larger decrease in forelimb grip strength (18%). Thus, ECHA considers that the data you provided substantiates ECHA's concerns about the grip strength effect. Additionally, ECHA considers that the 422 study does not outweigh the results of the 90-day study, in view of the shorter time period and reduced statistical power of the 422 study.

(4) You argue that the finding in the recovery group in motor activity is 'purely casual' because of the single occasion, the late occurrence, [and] the lack of other neurological signs at that given time point. You also note that another measure of activity, rearing, "showed statistically significant variations of treated groups when compared to controls", but you consider these changes not toxicologically significant.

ECHA agrees that, by itself, the finding on motor activity would not be sufficient concern. However, there are several other issues which do give rise to concern and this single, statistically significant finding cannot be disregarded. The motor activity finding therefore supports the overall concern for developmental neurotoxicity.

ECHA therefore concludes that the developmental neurotoxicity Cohorts 2A and 2B need to be conducted because there is a particular concern on (developmental) neurotoxicity based on the results from the above-identified *in vivo* study on the registered substance.

Additionally, ECHA notes that several Member States have in their PfAs identified concerns based on potential constituents of the registered substance. In principle, the presence of a significant amount of a neurotoxic constituent in a particular batch of the registered substance could determine the neurotoxic effects of that particular batch of the registered substance. In this regard, the lack of analytical information on the registered substance as tested in the 90-day study is a significant limitation in assessing the hazardous nature of the registered substance. ECHA notes the importance of characterising the composition of test substance, as set out in Appendix 3, point 4.

Species and route selection

According to the test method OECD TG 443, the rat is the preferred species. On the basis of this default assumption, ECHA considers that testing should be performed in rats.

ECHA considers that the oral route is the most appropriate route of administration for substances except gases to focus on the detection of hazardous properties on reproduction as indicated in ECHA *Guidance on information requirements and chemical safety assessment* (version 6.0, July 2017) Chapter R.7a, Section R.7.6.2.3.2. Since the substance to be tested is a liquid, ECHA concludes that testing should be performed by the oral route.

Outcome

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, you are requested to submit the following information derived with the registered substance subject to the present decision: Extended one-generation reproductive toxicity study (test method OECD TG 443), in rats, oral route, according to the following study-design specifications:

- Ten weeks premating exposure duration for the parental (P0) generation;
- Dose level setting shall aim to induce systemic toxicity at the highest dose level;
- Cohort 1A (Reproductive toxicity);
- Cohort 1B (Reproductive toxicity) with extension to mate the Cohort 1B animals to produce the F2 generation; and
- Cohorts 2A and 2B (Developmental neurotoxicity).

While the specifications for the study design are given above, you shall also submit with the new endpoint study record a scientific justification on each of the following aspects: 1) length of the premating exposure duration and dose level selection, 2) reasons for why or

why not Cohort 1B was extended, 3) termination time for F2 generation, and 4) reasons for why or why not Cohorts 2A/2B and/or Cohort 3 were included.

Notes for your consideration

The Agency considers that the considerations made by the Member State authority summarised above are not sufficient to show that the triggers for the inclusion of Cohort 3 (developmental immunotoxicity) has been met. However, you may expand the study by including Cohort 3 if new information becomes available after this decision is issued to justify such an inclusion. Inclusion is justified if the available information, together with the new information shows triggers which are described in column 2 of Section 8.7.3., Annex X and further elaborated in ECHA *Guidance on information requirements and chemical safety assessment* Chapter R.7a, Section R.7.6 (version 6.0, July 2017). You may also expand the study to address a concern identified during the conduct of the extended one-generation reproduction toxicity study and also due to other scientific reasons in order to avoid a conduct of a new study. The justification for the expansion must be documented.

Appendix 2: Procedural history

For the purpose of the decision-making, this decision does not take into account any updates of your registration after the date when the draft decision was notified to you under Article 50(1) of the REACH Regulation.

On 19 May 2017 ECHA issued decision CCH-D-2114360325-54-01/F.

On 12 July 2018 the registrant provided a 90-day sub-chronic toxicity study.

On 30 July 2018 ECHA consulted the Member State authorities asking for their opinion whether the design of the extended one-generation reproductive toxicity study requested in decision CCH-D-2114360325-54-01/F should be revised. One Member State informed ECHA that the design of the extended one-generation reproductive toxicity study needed to be reviewed.

On 12 October 2018 ECHA therefore informed the registrant that the request for an extended one-generation reproductive toxicity study in decision CCH-D-2114360325-54-01/F was withdrawn and would be addressed in this separate decision.

The compliance check of the information requirement for an extended one-generation reproductive toxicity study was initiated on 12 October 2018.

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

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

ECHA did not receive any comments by the end of the commenting period.

ECHA notified the draft decision to the competent authorities of the Member States for proposal(s) for amendment.

ECHA received proposals for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendments.

ECHA referred the draft decision to the Member State Committee.

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

The Member State Committee reached a unanimous agreement on the draft decision in its MSC-64 written procedure and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix 3: Further information, observations and technical guidance

1. The substance subject to the present decision is provisionally listed in the Community rolling action plan (CoRAP) for the start of substance evaluation in 2020.

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

3. Failure to comply with the requests in this decision will result in a notification to the enforcement authorities of your Member State.

4. While selecting the test material you must take into account the impact of each constituent/impurity on the test results for the endpoint to be assessed. For example, if a constituent/impurity of the Substance is known to have an impact on (eco)toxicity, the selected test material must contain that constituent/impurity. Any constituents that have harmonised classification and labelling according to the CLP Regulation (Regulation (EC) No 1272/2008) must be identified and quantified using the appropriate analytical methods.

The OECD Series on Principles of Good Laboratory Practice and Compliance Monitoring, Number 11 [ENV/MC/CHEM(98)16] requires a careful identification of the test material and description of its characteristics. In addition, the Test Methods Regulation (EU) 440/2008, as amended by Regulation (EU) 2016/266, requires that "*if the test method is used for the testing of a* [...] *UVCB* [...] *sufficient information on its composition should be made available, as far as possible, e.g. by the chemical identity of its constituents, their quantitative occurrence, and relevant properties of the constituents*".

In order to meet this requirement, all the constituents of the test material used for each test shall be identified as far as possible. For each constituent the concentration value in the test material shall be reported in the Test material section of the endpoint study record.

Technical Reporting of the test material for UVCB substances

The composition of the selected test material must be reported in the respective endpoint study record, under the Test material section. The composition must include all constituents of the test material and their concentration values. Without such detailed reporting, ECHA may not be able to confirm that the test material is relevant for the Substance and to all the registrants of the Substance.

Technical instructions are available in the manual "How to prepare registration and PPORD dossiers" on the ECHA website[6].

[6] https://echa.europa.eu/manuals