~~Confidential~~

Helsinki, 27 October 2020

Addressees
Registrant(s) of [redacted] as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
23/05/2013

Registered substance subject to this decision ("the Substance")
Substance name: Phenol
EC number: 203-632-7
CAS number: 108-95-2

Decision number: Please refer to the REACH-IT message which delivered this communication (in format CCH-D-XXXXXXXXXX-XX-XX/F)

DECISION ON A COMPLIANCE CHECK

Under Article 41 of Regulation (EC) No 1907/2006 (REACH), you must submit the information listed below, by the deadline of ***2 August 2022***.

Requested information must be generated using the Substance unless otherwise specified.

A. Information required from all the Registrants subject to Annex X of REACH

1. Transgenic rodent somatic and germ cell gene mutation assay (Annex X, Section 8.4., column 2; test method: OECD TG 488 from 2020[1]) in transgenic mice or rats, oral route, on the following tissues: liver and glandular stomach; germ cells and duodenum must be harvested and stored for up to 5 years. Duodenum must be analysed if the results of the glandular stomach and of the liver are negative or inconclusive.

Reasons for the request are explained in the Appendix entitled "Reasons to request information required under Annexes X of REACH".

Information required depends on your tonnage band

You must provide the information listed above in accordance with Articles 10(a) and 12(1) of REACH, that is the information specified in Annexes VII to X to REACH, for registration at more than 1000 tpa.

You are only required to share the costs of information that you must submit to fulfil your information requirements.

How to comply with your information requirements

To comply with your information requirements you must submit the information requested by this decision in an updated registration dossier by the deadline indicated above. You must also update the chemical safety report, where relevant, including any changes to classification

[1] The updated OECD TG 488, adopted on 26 June 2020, is available on OECD website at https://www.oecd-ilibrary.org/docserver/9789264203907-en.pdf?expires=1596539942&id=id&accname=guest&checksum=D552783C4CB0FC8045D04C88EFFBFA66.

and labelling, based on the newly generated information.

You must follow the general testing and reporting requirements provided under the Appendix entitled "Requirements to fulfil when conducting and reporting new tests for REACH purposes". In addition, you should follow the general recommendations provided under the Appendix entitled "General recommendations when conducting and reporting new tests for REACH purposes". For references used in this decision, please consult the Appendix entitled "List of references".

Appeal

This decision, when adopted under Article 51 of REACH, may be appealed to the Board of Appeal of ECHA within three months of its notification to you. Please refer to http://echa.europa.eu/regulations/appeals for further information.

Failure to comply

If you do not comply with the information required by this decision by the deadline indicated above, ECHA will notify the enforcement authorities of your Member State.

Authorised[2] under the authority of Christel Schilliger-Musset, Director of Hazard Assessment

[2] 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 A: Reasons to request information required under Annex X of REACH

1. Transgenic rodent somatic and germ cell gene mutation assays (Annex X, Section 8.4., column 2)

Under Annex X to REACH, the information requirement for a second *in vivo* somatic cell genotoxicity study is triggered if there is a positive result in any of the *in vitro* genotoxicity studies in Annex VII or VIII, but also depending on the quality and relevance of all the available data.

Your dossier contains positive results for the *in vitro* cytogenicity tests and *in vitro* gene mutation study in mammalian cells, which raise both concerns, i.e. gene mutation and chromosomal aberration.

Also, your dossier contains the following *in vivo* studies:

i. Several rodent bone marrow micronucleus tests with mice, including the studies and publications from Ciranni *et al.* (1988), McFee *et al.* (1991), Spencer *et al.*, (2003 and 2007), [redacted] (2005), Gad-El Karim *et al.* (1985 and 1986), Gocke *et al.* (1981), Chen and Eastmond (1995), Shelby *et al.* (1993) and Marrazzini *et al.* (1994);
ii. Rodent bone marrow chromosomal aberration test with rats from Thompson and Gibson (1984);
iii. Sex-linked recessive lethal assays in *Drosophila melanogaster*, including the study from Woodruff *et al.* (1985);
iv. DNA strand break test in testes of rats from, Skare and Schrotel (1984);
v. DNA damage tests in rats, including the study from Reddy *et al.* (1990);
vi. DNA damage test in mice from Kolachana *et al.* (1993);
vii. *In vitro-in vivo* replicative DNA synthesis test in rats from Takasawa *et al.* (1994);
viii. *In vitro-in vivo* replicative DNA synthesis test in mice from Miyagawa *et al.* (1995); and
ix. Induction of LacZ-mutations in tissues of treated Muta-TM mice, inhalation and dermal routes, Rel. 3, GLP compliant, no test guideline followed, HSE (1999; final report in 2006).

Although you do not explicitly claim an adaptation, ECHA understands that studies iii. to ix. were submitted in order to meet the information requirement by means of adaptation according to Annex XI, Section 1.1.2. This adaptation rule enables registrants to claim that the data from experiments not carried out according to GLP or the test methods referred to in Article 13(3) can be considered equivalent to data generated by those test methods.

We have assessed this information and identified the following issues:

a. Studies i. and ii. addressing chromosal aberration only:

The ECHA guidance R.7a[3] states that a second *in vivo* test is required "if *the in vitro* data show the substance to have potential to induce both gene and chromosome mutations and the first *in vivo* test has not addressed this comprehensively".

As indicated above, in your dossier there are positive *in vitro* results that raise concerns for both gene mutations and chromosomal aberrations. However, studies i. and ii. address only the chromosomal aberrations concern.

Therefore these *in vivo* studies are not sufficient to address both concerns.

[3] ECHA Guidance R.7a, section R.7.7.6.3, p.570.

b. Non-guideline studies iii. not adequate:

The adaptation rule in Annex XI, Section 1.1.2 imposes a number of cumulative conditions for an adaptation to be valid, in particular:

- Adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3), in this case OECD TG 488 or 489;
- Exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3);
- Adequacy for the purpose of classification and labelling and/or risk assessment.

OECD TG 488 or 489, require testing in mammalian cells (rodent species) as a key parameter.

However, the studies iii. do not address gene mutation in mammalian cells. The tests were performed with insects and not with mice or rats (as required in OECD TGs 488 and 489).

Therefore the *in vivo* studies iii. are not adequate.

c. Non-GLP, non guideline studies iv. to viii. not adequate:

The adaptation rule in Annex XI, Section 1.1.2 imposes a number of cumulative conditions for an adaptation to be valid, in particular:

- Adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3), in this case OECD TG 489;
- Exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3);
- Adequacy for the purpose of classification and labelling and/or risk assessment.

The key parameters of OECD TG 489 include that:

a) The study must include a negative control group, a positive control group, and a minimum of three treated groups.
b) Each group must have a minimum of 5 analysable animals (the test can be performed in either sex).
c) At least 150 cells must be analysed for each sample (per tissue, per animal).
d) The highest dose studied must be the maximum tolerated dose (MTD), i.e. the highest dose that induces slight toxic effects relative to the duration of the study period (e.g. body weight depression or hematopoietic system cytotoxicity, but not death or evidence of pain, suffering or distress necessitating euthanasia).
e) Data on the % tail DNA (or other measures, if chosen) and mean values per group should be reported for the treated and control groups.

Studies iv. to viii. provide indication of induced damage to DNA via effects such as DNA strand breaks and DNA adduct formation. The above mentioned key parameters are not met, because the reported data for the studies do not include:

a) the appropriate number of doses
b) a negative control with a response inside the historical control range of the laboratory.
c) a positive control group (or scoring control)
d) the appropriate number of analysable animals
e) the analysis of the adequate number of cells
f) a maximum studied dose that is a MTD or induces toxicity
g) data on the % tail DNA (or other measures, if chosen) and mean values per group for

the treated and control groups.

Therefore the *in vivo* studies iv. to viii. are not adequate.

d. Non-guideline studies under ix. not adequate:

The adaptation rule in Annex XI, Section 1.1.2 imposes a number of cumulative conditions for an adaptation to be valid, in particular:

- Adequate and reliable coverage of the key parameters foreseen to be investigated in the corresponding test methods referred to in Article 13(3), in this case OECD TG 488;
- Exposure duration comparable to or longer than the corresponding test methods referred to in Article 13(3);
- Adequacy for the purpose of classification and labelling and/or risk assessment.

The key parameters of OECD TG 488 include:
a) The study must include a minimum of three doses/groups of treated animals as well as a negative control group and a positive control group.
b) The highest dose studied must be the maximum tolerated dose (MTD), i.e. the highest dose that produce signs of toxicity but no lethality (e.g. body weight depression or hematopoietic system cytotoxicity, but not death or evidence of pain, suffering or distress necessitating humane euthanasia).
c) A repeated-dose regimen is necessary, with daily treatments for a period of 28 days.
d) Data on the mutation frequency for each tissue and for the treated and control groups must be reported.

In the dossier, you provided two *in vivo* studies (studies under ix. above), with a Klimish score of 3 (not reliable). You indicated that the studies under ix. are "*transgenic mouse mutation assays*". The above mentioned key parameters are not met, because the reported data for the studies do not include:
a) the appropriate number of doses
b) a maximum studied dose that is a MTD or induces toxicity
c) the sufficient exposure duration
d) data on the mutation frequency for each tissue and for the treated and control groups.

Therefore the *in vivo* tests provided under ix. are not adequate.

Based on the above, there is no adequate data to follow-up the gene mutation concern and therefore the information requirement for a second *in vivo* somatic cell genotoxicity study is triggered.

i. Test selection

According to the ECHA Guidance Chapter R.7a[4], the transgenic rodent somatic and germ cell gene mutation assays ("TGR assay", OECD TG 488) and the *in vivo* mammalian alkaline comet assay ("comet assay", OECD TG 489) are both suitable to follow up a *positive in vitro* result on gene mutation.

In your comments to the draft decision you indicate that you accept the information request and welcome that the selection between the two options is still open and that it is up to you to make the final selection.

[4] ECHA Guidance Chapter R.7a, Section R.7.7.6.3

However, a Member State competent authority made a proposal for amendment (PfA) to remove the option to perform the comet assay. ECHA agrees with the PfA.

The comet assay detects DNA damage arising from chromosomal aberration and from gene mutation, without distinguishing between these two mechanisms. Since the Substance is already known to cause mutations via chromosomal aberration, if the the comet assay would be positive, it would not provide direct evidence of the absence or of the presence of the gene mutation concern. By contrast, the TGR assay specifically detects gene mutations. Therefore, in the current case, the TGR assay is the only test which is appropriate to address the gene mutation concern specifically.

ii. Test design

According to the test method OECD TG 488, the test must be performed in transgenic mice or rats and the test substance is usually administered orally.

Based on the recent update[5] of OECD TG 488, you are requested to follow the new 28+28d regimen, as it permits the testing of mutations in somatic tissues and as well as in tubule germ cells from the same animals. This updated version provides for a transitional period for the new version. However, ECHA is aware that testing according to the updated OECD TG is already available from CROs and the new study design would provide meaningful germ cell data, so this decision requires the application of the new version.

According to the test method OECD TG 488, the test must be performed by analysing tissues from liver as slowly proliferating tissue and primary site of xenobiotic metabolism, glandular stomach and duodenum as rapidly proliferating tissue and site of direct contact. There are several expected or possible variables between the glandular stomach and the duodenum (different tissue structure and function, different pH conditions, variable physico-chemical properties and fate of the Substance, and probable different local absorption rates of the Substance and its possible breakdown product(s)). In light of these expected or possible variables, it is necessary to analyse both tissues to ensure a sufficient evaluation of the potential for mutagenicity at the site of contact in the gastro-intestinal tract. However, duodenum must be stored (at or below −70 °C) until the analysis of liver and glandular stomach is completed; the duodenum must then be analysed only if the results obtained for the glandular stomach and for the liver are negative or inconclusive.

iii. Germ cells

A subsequent germ cell genotoxicity study (TGR/OECD TG 488, or CA on spermatogonia/OECD TG 483, depending on the concern raised by the substance) may still be required under Annex X of REACH, in case 1) an *in vivo* genotoxicity test on somatic cell is positive, and 2) no clear conclusion can be made on germ cell mutagenicity.

ECHA notes that according to the OECD 488 the tissues (or tissue homogenates) can be stored under specific conditions and used for DNA isolation for up to 5 years. Hence, in order to limit additional animal testing male germ cells must be collected (from the seminiferous tubules) at the same time as the other tissues (liver, glandular stomach and duodenum), and stored up to 5 years (at or below −70 °C). This duration is sufficient to allow you or ECHA, in accordance with Annex X, Section 8.4., column 2, to decide on the need for assessment of mutation frequency in the collected germ cells.

[5] The updated OECD TG 488, adopted on 26 June 2020, is available on OECD website at https://www.oecd-ilibrary.org/docserver/9789264203907-en.pdf?expires=1596539942&id=id&accname=guest&checksum=D552783C4CB0FC8045D04C88EFFBFA66

This type of evidence may be relevant for the overall assessment of possible germ cell mutagenicity including classification and labelling according to the CLP Regulation.

In your comments to the PfA you agreed to conduct the TGR assay (OECD TG 488) according to updated test guideline following a 28+28d dosing and sampling regime, and to include the collection of germ cells.

Appendix B: Requirements to fulfil when conducting and reporting new tests for REACH purposes

A. Test methods, GLP requirements and reporting

1. Under Article 13(3) of REACH, all new data generated as a result of this decision must be conducted according to the test methods laid down in a European Commission Regulation or to international test methods recognised by the Commission or ECHA as being appropriate.

2. Under Article 13(4) of REACH, ecotoxicological and toxicological tests and analyses must be carried out according to the GLP principles (Directive 2004/10/EC) or other international standards recognised by the Commission or ECHA.

3. Under Article 10(a)(vi) and (vii) of REACH, all new data generated as a result of this decision must be reported as study summaries, or as robust study summaries, if required under Annex I of REACH. See ECHA Practical Guide on How to report robust study summaries[6].

B. Test material

Before generating new data, you must agree within the joint submission on the chemical composition of the material to be tested (Test Material) which must be relevant for all the registrants of the Substance.

1. Selection of the Test material(s)
   The Test Material used to generate the new data must be selected taking into account the following:
   - the variation in compositions reported by all members of the joint submission,
   - the boundary composition(s) of the Substance,
   - 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.

2. Information on the Test Material needed in the updated dossier
   - You must report the composition of the Test Material selected for each study, under the "Test material information" section, for each respective endpoint study record in IUCLID.
   - The reported composition must include all constituents of each Test Material and their concentration values and other parameters relevant for the property to be tested.

This information is needed to assess whether the Test Material is relevant for the Substance and whether it is suitable for use by all members of the joint submission.

Technical instructions on how to report the above is available in the manual on How to prepare registration and PPORD dossiers[7].

[6] https://echa.europa.eu/practical-guides
[7] https://echa.europa.eu/manuals

Appendix C: Procedure

The Substance is listed in the Community rolling action plan (CoRAP) where substance evaluation started in 2015.

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

ECHA followed the procedure detailed in Articles 50 and 51 of REACH.

The compliance check was initiated on 13 February 2020.

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

In your comments you agreed to the draft decision. ECHA took your comments into account and did not amend the request and the deadline.

The timeline indicated in the draft decision to provide the information requested is 18 months from the date of adoption of the decision. In your comments to the draft decision, you requested an extension of the timeline. You justified your request stating that due to the current situation there might be a possible impact on the limitation of experimental capacities which would lead to a significant delay in the performance of studies.

Following a request from ECHA to provide documentary evidence to substantiate the claim above, you indicated that the deadline of 18 months should be met. You indicated that there may be more constraints if you decide to perform the OECD TG 488.

Based on the above, ECHA has not modified the deadline of the decision.

ECHA notified the draft decision to the competent authorities of the Member States for proposals for amendment.

ECHA received proposals for amendment and modified the draft decision.

ECHA invited you to comment on the proposed amendments and referred the modified draft decision to the Member State Committee.

Your comments on the proposed amendments were taken into account by the Member State Committee.

The Member State Committee reached a unanimous agreement on the draft decision during its MSC-71 meeting and ECHA took the decision according to Article 51(6) of the REACH Regulation.

Appendix D: List of references - ECHA Guidance[8] and other supporting documents

Evaluation of available information
Guidance on information requirements and chemical safety assessment, Chapter R.4 (version 1.1., December 2011), referred to as ECHA Guidance R.4 where relevant.

QSARs, read-across and grouping
Guidance on information requirements and chemical safety assessment, Chapter R.6 (version 1.0, May 2008), referred to as ECHA Guidance R.6 where relevant.

Read-across assessment framework (RAAF, March 2017)[9]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[9]

Physical-chemical properties
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Toxicology
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

Environmental toxicology and fate
Guidance on information requirements and chemical safety assessment, Chapter R.7a (version 6.0, July 2017), referred to as ECHA Guidance R.7a in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7b (version 4.0, June 2017), referred to as ECHA Guidance R.7b in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.7c (version 3.0, June 2017), referred to as ECHA Guidance R.7c in this decision.

PBT assessment
Guidance on information requirements and chemical safety assessment, Chapter R.11 (version 3.0, June 2017), referred to as ECHA Guidance R.11 in this decision.

Guidance on information requirements and chemical safety assessment, Chapter R.16 (version 3.0, February 2016), referred to as ECHA Guidance R.16 in this decision.

Data sharing
Guidance on data-sharing (version 3.1, January 2017), referred to as ECHA Guidance on data sharing in this decision.

OECD Guidance documents[10]

[8] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[9] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[10] http://www.oecd.org/chemicalsafety/testing/series-testing-assessment-publications-number.htm

Guidance Document on aqueous-phase aquatic toxicity testing of difficult test chemicals – No 23, referred to as OECD GD 23.

Guidance document on transformation/dissolution of metals and metal compounds in aqueous media – No 29, referred to as OECD GD 29.

Guidance Document on Standardised Test Guidelines for Evaluating Chemicals for Endocrine Disruption – No 150, referred to as OECD GD 150.

Guidance Document supporting OECD test guideline 443 on the extended one-generation reproductive toxicity test – No 151, referred to as OECD GD 151.

Appendix E: Addressees of this decision and the corresponding information requirements applicable to them

You must provide the information requested in this decision for all REACH Annexes applicable to you.

Registrant Name	Registration number	Highest REACH Annex applicable to you
[redacted]	[redacted]	[redacted]

Note: Where applicable, the name of a third party representative (TPR) may be displayed in the list of recipients whereas ECHA will send the decision to the actual registrant.