~~Confidential~~

Helsinki, 05 May 2022

Addressees
Registrants of 4-aminophenol as listed in the last Appendix of this decision

Date of submission of the dossier subject to this decision
27/03/2020

Registered substance subject to this decision ("the Substance")
Substance name: 4-aminophenol
EC number: 204-616-2

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 ***12 February 2024***.

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

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

1. Mammalian spermatogonial chromosomal aberration test (triggered by Annex IX, Section 8.4., column 2; test method: OECD TG 483) by oral route, in mice

2. Pre-natal developmental toxicity study in a second species (triggered by Annex IX, Section 8.7.2., column 2; test method: OECD TG 414) by oral route, in a second species (rabbit)

Reasons for the request(s) are explained in the following appendix entitled "Reasons to request information required under Annex IX of REACH".

Information required depends on your tonnage band

You must provide the information listed above for all REACH Annexes applicable to you, and in accordance with Articles 10(a) and 12(1) of REACH:

- the information specified in Annexes VII, VIII and IX to REACH, for registration at 100-1000 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 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". 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[1] under the authority of Mike Rasenberg, Director of 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 A: Reasons to request information required under Annex IX of REACH

1. In vivo mammalian Spermatogonial chromosomal aberration test

Under Annex IX, Section 8.4, column 2 of REACH, a germ cell genotoxicity investigation must be considered if two conditions are fulfilled: 1) an *in vivo* genotoxicity test on somatic cell is positive, and 2) no clear conclusion can be made on germ cell mutagenicity on the basis of all available data.

In relation to the condition 1) above, your dossier contains positive results in *in vivo* mammalian micronucleus tests (OECD TG 474, 1992 and 2007), which raise the concern for chromosomal aberration *in vivo*. Moreover, there is an *in vivo* chromosomal aberration test (OECD TG 475, 2000) with ambiguous test results.

In relation to the condition 2) above, your dossier contains a germ cell genotoxicity study, i.e. an *in vivo* germ cell dominant lethal test (1989).

We have assessed this information and identified the following issue(s):

To be considered adequate, the study has to meet the requirements of OECD TG 478 and the key parameters of this test guideline include:

a) That concurrent positive control animals must always be used unless the laboratory has demonstrated proficiency in the conduct of the test and has used the test routinely in the recent past (e.g. within the last 5 years).

   You did not provide any information regarding use of positive control for your study or the laboratory's proficiency in the conduct of the test.

b) The positive control substances should be known to produce dominant lethal mutations (DLs) under the conditions used for the test. Except for the treatment, animals in the control groups should be handled in an identical manner to animals in the treated groups.

   However, in your dossier you did not provide any data on whether a positive control induced DLs in your study. In your comments to the draft decision, you do not either provide any specific information addressing the issues identified above for the *in vivo* dominant lethal test (OECD TG 478).

As explained above, the information provided does not cover key parameters required by OECD TG 478.

Moreover, ECHA notes that the Substance has a harmonised classification as germ cell mutagen category 2 according to CLP, supporting the need to investigate further (see ECHA Guidance R.7a, section R.7.7.6.3, p.573), and that you have not provided toxicokinetic data nor your considerations for germ cell mutagenicity.

In your comments to the draft decision, you refer to toxicokinetic data, also available in your dossier, indicating that the test substance is absorbed and metabolised in mice. You also state that the Substance and/or its metabolite(s) can be considered to reach the gonads.
However, while your Substance can be considered to reach the gonads, no clear conclusion on the germ cell mutagenicity can be made based on the provided *in vivo* germ cell study for the reasons already explained above. Therefore, your justification is not valid and an *in vivo* germ cell test (OECD TG 483) is needed to fulfil the information requirement.

Based on the above there is no clear conclusion on germ cell mutagenicity. Therefore, as the conditions 1) and 2) explained above are met, ECHA concludes that an appropriate *in vivo* germ cell mutagenicity study is necessary to address the concern identified in somatic cells *in vivo*.

Information on study design

According to the ECHA guidance chapter R.*7a*[2] the Mammalian spermatogonial chromosome aberration test (OECD TG 483) is suitable to follow up a positive *in vivo* result showing chromosomal aberration in somatic cells.

Having considered the anticipated routes of human exposure and the need for adequate exposure of the target tissue(s) (see OECD TG 483, para. 29), performance of the test by the oral route is appropriate.

According to the test method OECD TG 483, mouse is the preferred species. However, other appropriate mammalian species may be used if scientifically justified (see OECD TG 483, para. 11).

In your comments to the draft decision, you claim that the requested mammalian spermatogonial chromosomal aberration test (OECD TG 483) is not part of the standard information requirements set out in Annex IX, section 8.4, column 2, and it is "*rarely performed*". You further state that contract research organisations (CROs) lack the experience, routine and control data for theses specific studies.

However, while an OECD TG 483 may not have to be systematically performed, Annex IX, section 8.4, column 2, requires to consider the potential for germ cell mutagenicity when triggered by positive *in vivo* studies in somatic tissues and based on evidence that the test substances, or a relevant metabolite, can reach the target tissue. Moreover, less animals are used in an OECD TG 483 study than in an OECD TG 478 study. Finally, you do not provide any evidence to substantiate your claim that CROs lack adequate experience to conduct such study.

2. Pre-natal developmental toxicity study in a second species

A Pre-natal developmental toxicity (PNDT) study (OECD TG 414) in one species is a standard information requirement under Annex IX to REACH. Annex IX, Section 8.7.2., column 2 provides that the decision on the need to perform a PNDT study on a second species at a tonnage level of 100 to 1000 tonnes per year should be based on the outcome of the PNDT study on a first species and all other relevant and available data.

You have provided

- a non-guideline 'Growth, Reproduction and Foetal Development' study (1989) in rats, via oral route, with the Substance;
- three non-guideline teratogenicity studies with Syrian golden hamster (1982) via oral, intraperitoneal and intravenous routes, respectively, with the Substance;
- an adaptation considering that a study in a second species is not warranted.

We have assessed this information and identified the following issues:

A. Triggering of the study in a second species

[2] ECHA Guidance R.7a, section R.7.7.6.3, p.573.

As mentioned above, a PNDT study on a second species is needed, if there is a concern for developmental toxicity based on the results from the PNDT study on a first species and other relevant data.

You consider that no developmental toxicity was observed in the available studies: '*A developmental and reproductive toxicity screening study performed according to GLP and OECD guidelines and several studies reported in the literature on the potential for developmental toxicity did not indicate that 4-aminophenol has the potential to be a reproductive or developmental toxicant*'.

However, taking all the available information into account as required in column 2 at Annex IX, section 8.7.2., there is a concern for developmental toxicity. The study on the first species (rat, 1989) showed an increase in the number of variations (for example unossified 5th or 6th sternebrae). Developmental toxicity was also observed in the available studies with Syrian golden hamster (1982) at dose levels which were not markedly toxic to dams. More specifically, the studies with intraperitoneal and intravenous administration reported an increased incidence of malformations in all treated animal groups. The observed effects included severe malformations such as neural tube defects. In addition, eye defects, limb defects, rib defects, tail defects and umbilical hernia were reported. The increased incidence of (severe) malformations in all treated groups, compared to controls, indicates a concern for prenatal developmental toxicity.

As the condition of Annex IX, section 8.7.2., column 2 is fulfilled, a pre-natal developmental toxicity study in two species is an information requirement for your registration. You have not provided an OECD TG 414 on a second species.

B. Assessment of the available studies in a second species

The 1989 study provides information on the first species, rats, and therefore does not fulfil the information requirement for a pre-natal developmental toxicity study in a second species. The non-guideline teratogenicity studies with Syrian golden hamster (1982) are assessed below.

In order to be considered compliant and enable assessing if the Substance is a developmental toxicant, the study has to meet the requirements of OECD TG 414. The criteria of this test guideline include e.g.

- 20 female animals with implantation sites for each test and control group,
- dosing of the Substance from implantation until the day prior to scheduled caesarean section,
- examination of the foetuses for sex and body weight as well as skeletal alterations (variations and malformations).

The studies you have provided (1982) were conducted with 2-6 pregnant females for each test group. The statistical power of the information provided is not sufficient because it does not fulfil the criterion of 20 pregnant females for each test group set in OECD TG 414.

In the studies you have provided (1982), the animals were exposed on GD 8 (a single dose). The study does not have a required exposure duration because the exposure duration is not from implantation until the day prior to scheduled caesarean section as required in OECD TG 414.

In the studies you have provided (1982) the sex and body weight of the foetuses has not been examined, and skeletal alterations (variations and malformations) have not been examined as required in OECD TG 414.

Based on the above, the information you provided for a second species do not fulfil the information requirement.

In the comments to the draft decision you recognize the limitations of the available hamster studies. However, you consider that a conclusion on the developmental toxicity potential of the Substance can be made based on available information and based on rapid and extensive metabolism of the Substance. However, in your comments you do not address the deficiencies identified with the studies in a second species provided in your dossier nor have you provided any new scientific information that could address the deficiencies.

On this basis the information requirement is not fulfilled.

Information on study design

A PNDT study according to the OECD TG 414 study should be performed in the rabbit or rat as the preferred species. The test in the first species was carried out by using a rodent species (rat). Therefore, a PNDT study in a second species must be performed in the rabbit as preferred non-rodent species.

The study shall be performed with oral[3] administration of the Substance.

[3] ECHA Guidance R.7a, Section R.7.6.2.3.2.

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[4].

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[5].

[4] https://echa.europa.eu/practical-guides
[5] https://echa.europa.eu/manuals

Appendix C: Procedure

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 12 March 2021.

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

ECHA took into account your comments and did not amend the requests.

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

As no amendments were proposed, ECHA adopted the decision under Article 51(3) of REACH.

Appendix D: List of references - ECHA Guidance[6] 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)[7]

RAAF - considerations on multiconstituent substances and UVCBs (RAAF UVCB, March 2017)[8]

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[9]

[6] https://echa.europa.eu/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment
[7] https://echa.europa.eu/support/registration/how-to-avoid-unnecessary-testing-on-animals/grouping-of-substances-and-read-across
[8] https://echa.europa.eu/documents/10162/13630/raaf_uvcb_report_en.pdf/3f79684d-07a5-e439-16c3-d2c8da96a316
[9] 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 their corresponding information requirements

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]
[redacted]	[redacted]	[redacted]

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.