EUROPEAN CHEMICALS AGENCY

Decision number: CCH-D-0000005300-89-02/F Helsinki, 16 September 2014

DECISION ON A COMPLIANCE CHECK OF A REGISTRATION PURSUANT TO ARTICLE 41(3) OF REGULATION (EC) NO 1907/2006

For acetophenone, CAS No 98-86-2 (EC No 202-708-7), registration number: [redacted]

Addressee: [redacted]

The European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 51 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

I. Procedure

Pursuant to Article 41(1) of the REACH Regulation ECHA has performed a compliance check of the registration for acetophenone, CAS No 98-86-2 (EC No 202-708-7), submitted by [redacted] (Registrant). The scope of this compliance check is limited to the standard information requirements of Annex IX, Sections 8.6.2. and 8.7.2. of the REACH Regulation. ECHA stresses that it has not checked the information provided by the Registrant and other joint registrants for compliance with requirements regarding the identification of the substance (Section 2 of Annex VI).

This decision is based on the registration as submitted with submission number [redacted], for the tonnage band of 100 to 1000 tonnes per year. This decision does not take into account any updates submitted after 12 June 2014, the date upon which ECHA notified its draft decision to the Competent Authorities of the Member States pursuant to Article 51(1) of the REACH Regulation.

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

The compliance check was initiated on 25 October 2013.

On 28 November 2013 ECHA sent the draft decision to the Registrant and invited him to provide comments within 30 days of the receipt of the draft decision. That draft decision was based on submission number [redacted]. On 13 January 2014 ECHA received comments from the Registrant on the draft decision. On 9 April 2014 the Registrant updated his registration dossier with the submission number [redacted].

The ECHA Secretariat considered the Registrant's comments and update. On basis of this information, Section II was amended. The Statement of Reasons (Section III) was changed accordingly.

On 12 June 2014 ECHA notified the Competent Authorities of the Member States of its draft decision and invited them pursuant to Article 51(1) of the REACH Regulation to submit proposals for amendment of the draft decision within 30 days of the receipt of the notification.

As no proposal for amendment was submitted, ECHA took the decision pursuant to Article 51(3) of the REACH Regulation.

II. Information required

Pursuant to Articles 41(1), 41(3), 10(a)(vii), 12(1)(d), 13 and Annex IX of the REACH Regulation the Registrant shall submit the following information using the indicated test methods and the registered substance subject to the present decision:

1. Sub-chronic toxicity study (90-day), oral route (Annex IX, 8.6.2.; test method: EU B.26./OECD 408) in rats;

2. Pre-natal developmental toxicity study (Annex IX, 8.7.2.; test method: EU B.31./OECD 414) in rats or rabbits, oral route.

Pursuant to Article 41(4) of the REACH Regulation the Registrant shall submit the information in the form of an updated registration to ECHA by **23 September 2016**. The timeline has been set to allow for sequential testing as appropriate.

Note for consideration by the Registrant:

The Registrant may adapt the testing requested above according to the specific rules outlined in Annexes VI to X and/or according to the general rules contained in Annex XI of the REACH Regulation. In order to ensure compliance with the respective information requirement, any such adaptation will need to have a scientific justification, referring to and conforming with the appropriate rules in the respective Annex, and an adequate and reliable documentation.

Failure to comply with the request(s) in this decision, or to fulfil otherwise the information requirement(s) with a valid and documented adaptation, will result in a notification to the Enforcement Authorities of the Member States.

III. Statement of reasons

Pursuant to Article 41(3) of the REACH Regulation, ECHA may require the Registrant to submit any information needed to bring the registration into compliance with the relevant information requirements.

Pursuant to Articles 10(a)(vii), 12(1)(d) of the REACH Regulation, a technical dossier for a substance manufactured or imported by the Registrant in quantities of 100 to 1000 tonnes per year shall contain as a minimum the information specified in Annex IX of the REACH Regulation.

In the updated registration, the Registrant has adapted the standard information requirements for a sub-chronic toxicity study (90-day) (Annex IX, Section 8.6.2.) and a pre-natal developmental toxicity study (Annex IX, Section 8.7.2.); by applying a read-across adaptation following REACH Annex XI, Section 1.5. The read-across approach is reflected in the following section.

0. Grouping of substances and read-across approach

Article 13(1) of the REACH Regulation provides that information on intrinsic properties of substances may be generated by means other than tests. Such other means include the use

of information from structurally related substances (grouping of substances and read-across), "*provided that the conditions set out in Annex XI are met*".

Annex XI, 1.5. requires a structural similarity among the substances within a group or category such that relevant properties of a substance within the group can be predicted from the data on reference substance(s) within the group by interpolation. The following analysis presents the Registrant's justification for the proposed grouping approach and read-across hypothesis, together with ECHA's analysis concerning the justification in both a generic and an endpoint-specific context.

a. Introduction of the read-across approach proposed by the Registrant

The Registrant indicated that the target chemical is acetophenone. The analogue for the read across (source substance) is benzoic acid, one of the main metabolite of acetophenone. During the metabolic process, benzoic acid is the result of the oxidation and decarboxylation of acetophenone. In addition of sharing a common metabolic pathway, the target and the source substances are very close regarding their chemical structural and their properties.

The Registrant notes that benzoic acid has been assessed in various international regulatory programs and many data are available on this substance or other benzoates in the same category like REACH registration dossier, OECD SIDS Dossier on Benzoates, EU opinion (SCF), JECFA, BUA report, FEMA GRAS assessment, BIBRA. Thus the basis for the read across approach as proposed by the Registrant is the common metabolic pathway and a similarity in chemical structure and properties.

b. Information submitted by the Registrant to support the read-across approach

In the initial submitted registration, the Registrant has provided an OECD 422 screening study and a 17 week oral toxicity study with the registered substance acetophenone to cover the information requirement for sub-chronic toxicity (90-day). In the updated registration, the Registrant provided further information performed with metabolites of acetophenone. One is a publication from Kieckebusch and Lang (1960) describing a 3-generation study in rats with dietary administration of benzoic acid. Furthermore, the Registrant has provided a publication from Yukio and Makoto (1979) describing a carcinogenicity study in rats with dietary administration of sodium benzoate.

In the updated registration, the Registrant has provided further information to cover the endpoint pre-natal developmental toxicity. One publication from Onodera et al. (1978) investigated the effect of sodium benzoate in rat fetuses and offspring. The other four studies from FDA (1972) investigated the teragogenicity of sodium benzoate in mice, rats, hamsters and rabbits.

A read-across justification document was provided by the Registrant together with the comments to the draft decision. In this read-across justification the following arguments were provided by the Registrant to support read-across:

i. Source substance

The source substance is benzoic acid (EC 200-618-2). Degree of impurity is [redacted] and [redacted] (w/w) with a typical concentration of [redacted]% (w/w). Impurities are [redacted] and benzene [redacted]% w/w).

ii. Metabolic pathway

The Registrant provided information on metabolism of acetophenone. The Registrant argues that as acetophenone seems to be rapidly absorbed, transformed to benzoic acid, and rapidly excreted in the urine as hippuric acid, the read-across approach is scientifically justified. Benzoic acid is part of a chemical category (Benzoates), and data on its sodium salt are also relevant for this read-across. According to the Registrant, the category "Benzoates" is justified by the fact that the chemical members share the same metabolic pathway and the dominant species is the ionic form (i.e. benzoate ion) at physiological pH (with pKa of 4.2). Even if other metabolites (mandelic acid, phenylglyoxylic acid) are formed after exposure to acetophenone, the Registrant does not consider this to affect the validity of this read-across. The Registrant notes that these co-metabolites are structurally similar to benzoic acid and share similar functional groups. Even if few data are available on mandelic acid (CAS 90-64-2) and phenylglyoxylic acid (CAS 611-73-4), the Registrant concludes that it can be assumed that their properties will not be significantly different from those related to benzoic acid.

iii. Properties

The Registrant assumes that even if the source chemical (a carboxylic acid) has a carbonyl group and an alcohol group and share some basic physico-chemical properties with ketones, the combination of a carbonyl and an alcohol group results however in some specific chemical properties: beside acidity (the most notable of them), carboxylic acids have relatively high boiling points and relatively high water solubility when compared with the corresponding ketone (explained by a higher polar organic functional group in carboxylic acids). According to the Registrant, this property can also influence the vapour pressure, lower in benzoic acid. However these variations are not expected to affect the validity of this read-across approach. Regarding the toxicological properties, the Registrant concludes that the results presented in Chapter 5 suggest similar systemic toxicity profiles for both substances and thus support the proposed read-across. The Registrant notes that the conclusion is different for the local toxicity, as the source substance is considered as corrosive (classified Skin Irrit. 2; Eye Dam. 1 according to CLP criteria). However as the scope of the read-across does not include the irritation/corrosion endpoint, it does not impact the read-across approach according to the Registrant.

iv. Data matrix

The Registrant has provided a data matrix. The Registrant stated that all the data from the source substance (benzoic acid) have been collected from the disseminated REACH registration dossier. The Registrant has assessed all the data as reliable and considered them as relevant for the read across. The Registrant also indicated that most of the data were peer-reviewed and published in high quality scientific literature and most of them have been reviewed and accepted by other organisations like FDA, JECFA, and IPCS. In the data matrix, the Registrant compared the information for acetophenone and benzoic acid with respect to chemical characteristics, classification and labelling, physico-chemical data, key environment and pathway endpoints and on all toxicology endpoints including repeated dose toxicity and pre-natal developmental toxicity.

c. ECHA analysis of the read-across approach in light of the requirements of Annex XI, 1.5.

ECHA acknowledges that one of the products resulting from the metabolism of the registered substance acetophenone may be benzoic acid. The Registrant claims that the metabolism from acetophenon to benzoic acid is rapid, but does not provide toxicokinetic evidence for this claim. ECHA considers that this particular metabolic pathway requires

several metabolic steps and intermediates are formed. It is likely that the parent compound as well as such intermediates are present in the systemic circulation for a considerable amount of time. Therefore, significant systemic exposure to the parent substance acetophenone and intermediates is likely. In addition, acetophenone may be metabolised via different pathways, e.g. via hydroxylation of the benzene ring, as indicated in Figure 1 of the provided read-across document. The Registrant does not address exposure to the parent compound, the intermediates or other metabolites in his read-across approach. He only states that such other metabolites do not affect the validity of the read-across. However, this claim is not supported by evidence, and it has to be assumed that metabolic products other than benzoic acid have influence on the toxicity profile of acetophenone. This assumption is supported by the observed differences in the toxicity profiles of acetophenone and benzoic acid (see below).

Furthermore, the Registrant addresses the difference in the functional groups that may result in different properties of the substances. The Registrant has addressed the difference in local toxicity with regard to irritation/corrosion but assumes that these structural differences are not expected to affect the validity of this read-across approach for systemic effects. This assumption is not substantiated by an explanation which addresses the relationship between these structural differences and possible systemic toxicity. In addition, ECHA notes that acetophenone significantly differs in its toxicity compared to benzoic acid or sodium benzoate: in the provided repeated dose toxicity studies with benzoic acid no effects were observed up to doses of 500 mg/kg bw/d, and with sodium benzoate, no effects were observed up to 1000 mg/kg bw/d. However, in the OECD 422 screening study with acetophenone, relevant clinical as well as neurobehavioral effects were observed at 750 mg/kg bw/d, resulting in a NOAEL of 250 mg/kg bw/d. Consequently, acetophenone seems to have different toxicological properties than benzoic acid or sodium benzoate.

d. ECHA analysis of the endpoint-specific read-across approach in light of the requirements of Annex XI, 1.5.

i. Sub-chronic toxicity (90-days)

As indicated above, the substances differ in their functional groups and show different toxicological properties with regard to repeated dose toxicity.

ECHA further notes that the provided repeated dose toxicity studies on benzoic acid and sodium benzoate have relevant shortcomings. For example, in the publication from Kieckebusch and Lang (1960) it is not reported if the organs for which the organ weight was examined (brain, heart, liver spleen, kidneys and testes), were also examined histopathological. In the carcinogenicity study from Yukio and Makoto (1979), no increased incidence for neoplastic effects were reported but no information on histopathological effects was given. Therefore, these studies do not adequately and reliably cover the key parameters (histopathological examination of indicated organs) of a sub-chronic toxicity study (90 days).

Consequently, the following requirement of Annex XI, Section 1.5. are not met: (i) the substances differ in their functional groups, (ii) the toxicological properties of the substances (repeated dose toxicity) are not likely to be similar, and (iii) the studies provided do not adequately and reliably cover the key parameters of a sub-chronic toxicity study (90 days). As a conclusion, the subchronic toxicity of acetophenone cannot be predicted on the basis of results obtained with benzoic acid.

ii. Pre-natal developmental toxicity

As indicated above, the substances differ in their functional groups and show different toxicological properties for repeated dose toxicity.

ECHA further observes that the substances also seem to differ with respect to developmental toxicity. For example, in a pre-natal devlopmental toxicity study with benzoic acid increased offspring mortality was observed at 1350 mg/kg bw/d. However, the screening study with acetophenone indicated "remarkable" effects on the offspring like increased stillborn pups, pup mortality and individual cases of cleft palate, edema, atelectasis, milk not present in the stomach and dermal hypoplasia) already at 750 mg/kg bw/d. Therefore, acetophenone seems to be more potent with regard to developmental toxicity than benzoic acid. Therefore, the toxicological properties of the substances with respect to pre-natal developmental toxicity are not likely to be similar.

Furthermore, ECHA observes that in the other pre-natal developmental toxicity studies with benzoic acid in various species, the doses tested were not high enough to induce any maternal toxicity; for example, the highest dose used in the rat study was 175 mg/kg bw/d. OECD test method 414 requires that the highest dose should induce some developmental and/or maternal toxicity. Therefore, those studies do not cover an important key parameter of a pre-natal developmental toxicity study.

Consequently, the following requirement of Annex XI, Section 1.5. are not met: (i) the substances differ in their functional groups, (ii) the toxicological properties of the substances (pre-natal developmental toxicity) are not likely to be similar, and (iii) some provided studies do not adequately and reliably cover a relevant key parameter of a pre-natal developmental toxicity study. As a conclusion, the pre-natal developmental toxicity of acetophenone cannot be predicted on the basis of results obtained with benzoic acid.

e. Conclusion on the read-across approach

Pursuant to Article 41(1) of the REACH Regulation, ECHA concludes that the adaptation of the standard information requirements for the endpoints sub-chronic toxicity and pre-natal developmental toxicity in the technical dossier based on the proposed read-across approach does not comply with the general rules of adaptation as set out in Annex XI, 1.5. Therefore, ECHA rejects all adaptations in the technical dossier that are based on Annex XI, 1.5.

1. Sub-chronic toxicity study (90-day) (Annex IX, 8.6.2.)

A "sub-chronic toxicity study (90 day)" is a standard information requirement as laid down in Annex IX, Section 8.6.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

The Registrant has not provided any study record of a sub-chronic toxicity study (90 day) in the dossier that would meet the information requirement of Annex IX, Section 8.6.2.

The Registrant has sought initially to adapt this information requirement, claiming that there is sufficient weight of evidence demonstrating that there is no need for a sub-chronic toxicity study. More specifically: The Registrant has provided a study record for a "combined repeated dose toxicity study with the reproduction/developmental toxicity screening test" (test method: OECD 422) via the oral route of administration. However, this study does not provide the information required by Annex IX, Section 8.6.2., because exposure duration is

less than 90 days. The Registrant has further provided as supporting study ("weight of evidence") a publication "Hagan et al. 1967" using 17 weeks of dietary application of the substance. ECHA notes the relevant shortcomings of the publication by Hagan et al. 1967 which are indicated by the Registrant (missing documentation, relevant loss of substance). In fact these shortcomings prevent to assume or conclude in a weight of evidence approach according to Annex XI, Section 1.2., that the registered substance subject to the present decision has or has not a particular dangerous property after sub-chronic exposure. Therefore, the weight of evidence approach cannot be accepted.

In the comments to the draft decision and in the updated registration dossier, the Registrant has sought to adapt the required information by read-across. ECHA has evaluated the Registrant's read-across approach and concludes that it does not fulfil the requirement defined in Annex XI, 1.5. (see Section III, 0. above).

Consequently there is an information gap and it is necessary to provide information for this endpoint. Pursuant to Annex IX, Section 8.6.2., testing should be carried out by the most appropriate route of administration.

In the initial draft decision sent to the Registrant, ECHA requested testing via the inhalation route. With respect to the inhalation route, the Registrant indicated in the updated registration dossier that "*No sub-acute or sub-chronic repeated dose toxicity studies are available for inhalation route. However this study can be waived based on column 2 adaptation (Reach regulation, Annex VIII, section 8.6) and because exposure of humans via inhalation is unlikely; handling of the registered substance does not produce vapour, aerosols or droplets.*" The Registrant further indicates that in the registration on which the initial draft decision was based, industrial spraying and non-industrial spraying was mentioned. However, the Registrant indicated that since no user declared any longer use by aerosol/spray, the corresponding generic exposure scenarios initially presented in the chemical safety report have been deleted from the dossier in the update (submission number [redacted]) subject to the compliance check.

ECHA notes that the substance is a liquid with low vapour pressure, classified as eye irritating. Since the Registrant has removed any uses including aerosol/spray generation in the updated dossier, the inhalation route is no longer an appropriate route for testing. Therefore, the route was changed from inhalation to oral as most appropriate route of administration.

According to the test method OECD 413 the rat is the preferred species. ECHA considers this species as being appropriate and testing should be performed with the rat.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit the following information derived with the registered substance subject to the present decision: Repeated dose 90-day oral toxicity study (test method: EU B.26./OECD 408) in rats.

2. Pre-natal developmental toxicity study (Annex IX, 8.7.2.)

A "pre-natal developmental toxicity study" for a first species is a standard information requirement as laid down in Annex IX, Section 8.7.2. of the REACH Regulation. Adequate information on this endpoint needs to be present in the technical dossier for the registered substance to meet this information requirement.

The Registrant has not provided any study record of a pre-natal developmental toxicity study in the dossier that would meet the information requirement of Annex IX, Section 8.7.2.

In the comments to the draft decision and in the updated registration dossier, the Registrant has sought to adapt the required information by read-across. ECHA has evaluated the Registrant's read-across approach and concluded that it does not fulfil the requirement defined in Annex XI, 1.5. (see Section III, 0. above).

Therefore, the adaptation of the information requirement suggested by the Registrant cannot be accepted.

As explained above, the information available 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.

According to the test method EU B.31/OECD 414, the rat is the preferred rodent species, the rabbit the preferred non-rodent species and the test substance is usually administered orally. ECHA considers these default parameters appropriate and testing should be performed by the oral route with the rat or the rabbit as a first species to be used.

Therefore, pursuant to Article 41(1) and (3) of the REACH Regulation, the Registrant is requested to submit the following information derived with the registered substance subject to the present decision: Pre-natal developmental toxicity study (test method: EU B.31./OECD 414) in rats or rabbits by the oral route.

IV. Adequate identification of the composition of the tested material

ECHA stresses that the information submitted by the Registrant and other joint registrants for identifying the substance has not been checked for compliance with the substance identity requirements set out in Section 2 of Annex VI of the REACH Regulation . The Registrant is reminded of his responsibility and that of joint Registrants to ensure that the joint registration covers one substance only and that the substance is correctly identified in accordance with Annex VI, Section 2 of the REACH Regulation.

In relation to the information required by the present decision, the sample of substance used for the new studies must be suitable for use by all the joint registrants. Hence, the sample should have a composition that is within the specifications of the substance composition that are given by the joint registrants. It is the responsibility of all joint registrants who manufacture or import the same substance to agree on the appropriate composition of the test material and to document the necessary information on their substance composition.

In addition, it is important to ensure that the particular sample of substance tested in the new studies is appropriate to assess the properties of the registered substance, taking into account any variation in the composition of the technical grade of the substance as actually manufactured by each registrant. If the registration of the substance by any registrant covers different grades, the sample used for the new studies must be suitable to assess these grades.

Finally there must be adequate information on substance identity for the sample tested and the grade(s) registered to enable the relevance of the studies to be assessed.

V. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Article 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 ECHA's internet page at http://echa.europa.eu/appeals/app_procedure_en.asp. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

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