EUROPEAN CHEMICALS AGENCY

Helsinki, 20 May 2015

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

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

For furfuryl alcohol, CAS No 98-00-0 (EC No 202-626-1)

Addressees: Registrant(s)[1] of furfuryl alcohol (Registrant(s))

This decision is addressed to all Registrant(s) of the above substance with active registrations on the date on which the draft for the decision was first sent, with the exception of the cases listed in the following paragraph. A list of all the relevant registration numbers subject to this decision is provided as an enclosure to this decision.

Registrants holding active registrations on the day the draft decision was sent are *not* addressees of this decision if they are: i) Registrant(s) who had on that day registered the above substance exclusively as an on-site isolated intermediate under strictly controlled conditions and ii) Registrant(s) who have ceased manufacture/import of the above substance in accordance with Article 50(3) of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation) before the decision is adopted by ECHA.

Based on an evaluation by Bureau for Chemical Substances as the Competent Authority of Poland (evaluating MSCA), the European Chemicals Agency (ECHA) has taken the following decision in accordance with the procedure set out in Articles 50 and 52 of Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH Regulation).

This decision is based on the registration dossier(s) on 29 April 2014, i.e. the day on which the draft decision was notified to the Registrant(s) pursuant to Article 50(1) of the REACH Regulation.

This decision does not imply that the information provided by the Registrant(s) in the registration(s) is in compliance with the REACH requirements. The decision neither prevents ECHA from initiating compliance checks on the dossier(s) of the Registrant(s) at a later stage, nor does it prevent a new substance evaluation process once the present substance evaluation has been completed.

I. Procedure

Pursuant to Article 45(4) of the REACH Regulation the Competent Authority of Poland has initiated substance evaluation for furfuryl alcohol, CAS No 98-00-0 (EC No 202-626-1) based on registration(s) submitted by the Registrant(s) and other relevant and available information and prepared the present decision in accordance with Article 46(1) of the REACH Regulation.

On the basis of an opinion of the ECHA Member State Committee and due to initial grounds

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

for concern relating to human health/CMR, exposure/wide dispersive use, consumer use, high workers exposure, high release to the environment and aggregated tonnage, furfuryl alcohol was included in the Community rolling action plan (CoRAP) for substance evaluation to be evaluated in 2013. The updated CoRAP was published on the ECHA website on 20 March 2013. The Competent Authority of Poland was appointed to carry out the evaluation.

In the course of the evaluation, the evaluating MSCA noted additional concerns regarding the local toxicity via the inhalation route.

The evaluating MSCA considered that further information was required to clarify the above-mentioned concern. Therefore, it prepared a draft decision pursuant to Article 46(1) of the REACH Regulation to request further information. It submitted the draft decision to ECHA on 20 March 2014.

On 29 April 2014 ECHA sent the draft decision to the Registrant(s) and invited them pursuant to Article 50(1) of the REACH Regulation to provide comments within 30 days of the receipt of the draft decision.

Registrant commenting phase

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

The evaluating MSCA considered the comments received from Registrant(s). The information contained therein is reflected in the Statement of Reasons (Section III) whereas no amendments to the Information Required (Section II) were made.

Proposals for amendments by other MSCAs and ECHA

In accordance with Article 52(1) of the REACH Regulation, on 31 October 2014 the evaluating MSCA notified the Competent Authorities of the other Member States and ECHA of its draft decision and invited them pursuant to Articles 52(2) and 51(2) of the REACH Regulation to submit proposals to amend the draft decision within 30 days of the receipt of the notification.

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

On 5 December 2014 ECHA notified the Registrant(s) of the proposals for amendment to the draft decision and invited them pursuant to Articles 52(2) and 51(5) of the REACH Regulation to provide comments on those proposals for amendment within 30 days of the receipt of the notification.

The evaluating MSCA reviewed the proposals for amendment received and did not amend the draft decision.

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

By 5 January 2015, in accordance to Article 51(5), the Registrant(s) provided comments on the proposed amendments. The Member State Committee took into account the comments the Registrant(s) made on the proposals for amendment.

The Member State Committee, after discussion in its meeting on 3-5 February 2015, amended the information required (Section II) by removing the information request for a

28-day repeated dose toxicity study, which was part of the draft decision that was consulted with the MSCAs and ECHA in accordance with Article 52(1). Furthermore, it amended information required (Section II) by adding a request for an *in vivo* Mammalian Alkaline Comet Assay.

The Member State Committee reached a unanimous agreement on the draft decision as modified at the meeting on 5 February 2015.

ECHA took the decision pursuant to Article 51(6) of the REACH Regulation.

II. Information required

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

In Vivo Mammalian Alkaline Comet Assay (OECD test guideline 489) in mice, oral route, with examination of stomach, kidney and liver;

Pursuant to Article 46(2) of the REACH Regulation, the Registrant(s) shall submit to ECHA by 27 May 2016[2] an update of the registration(s) containing the information required by this decision, including robust study summaries and, where relevant, an update of the Chemical Safety Report.

III. Statement of reasons

Based on the evaluation of all relevant information submitted on furfuryl alcohol and other relevant and available information ECHA concludes that further information is required in order to enable the evaluating MSCA to complete the evaluation of whether the substance constitutes a risk to human health.

In Vivo Mammalian Alkaline Comet Assay (OECD test guideline 489) in mice, oral route, with examination of stomach, kidney and liver.

During the consultation with MSCAs, a proposal for amendment (PfA) was submitted to investigate concern for genotoxicity raised by positive results obtained on modified Salmonella typhimurium strains, in accordance with testing strategy proposed by MSCA. The Registrant(s) submitted comments to the PfA pointing out the results on modified Salmonella TA100 strain may be of value from mechanistic perspective but that positive results from these tests should not outweigh the results of negative findings of other data from established assays.

ECHA notes that most standard in vitro assays for gene mutation were negative for furfuryl alcohol. However, two modified Salmonella test strains show positive results. Monien et al. (2011[3]) studied mutagenicity using two different TA100-derived strains expressing human SULT1A1. As a result, mutagenicity increased in a dose-dependent manner up to more than 4 fold the solvent control value. According to the authors, the results of this study indicate

[2] *The deadline set by the decision already takes into account the time that registrants may require to agree on who is to perform any required tests and the time that ECHA would require to designate a registrant to carry out the test(s) in the absence of the aforementioned agreement by the registrants (Article 53(1) of the REACH Regulation).*

[3] *Monien et all, 2011. Metabolic activation of furfuryl alcohol: formation of 2-methylfuranyl DNA adducts in Salmonella typhimurium strains expressing human sulfotransferase 1A1 and in FVB/N mice. Carcinogenesis vol. 32 no. 10 pp. 1533-1539. Testing laboratory: Department of Nutritional Toxicology, German Institute of Human Nutrition (DifE) Potsdam Rehbrucke, 14558 Nuthetal, Germany.*

that furfuryl alcohol is metabolically converted to an electrophile metabolite reacting with DNA. In addition, two recent scientific studies have pointed to bioactivation of furfuryl alcohol by the enzyme sulfotransferase (Sachse et al. 2014a[4]; Sachse et al. 2014b[5]). Hence, there is a non-resolved concern for genotoxicity.

To clarify the concern for genotoxicity, comet assay should be conducted. The results of the comet assay are needed to clarify the concern of potential genotoxic effects resulting from bioactivation (sulfoconjugation) of furfuryl alcohol. It is recognized that "under alkaline conditions (>pH 13), the comet assay can detect single and double stranded breaks, resulting, for example, from direct interactions with DNA, alkali labile sites or as a consequence of transient DNA strand breaks resulting from DNA excision repair" (OECD TG 489). Moreover, comet assay proved to be of comparable performance in detecting the micronucleus-negative or equivocal carcinogens comparing to Transgenic rodent somatic and germ cell gene mutations assay (TGR) (Kirkland and Speit, 2008[6]), being also much less expensive than the potentially alternative TGR assay.

The study that showed most pronounced carcinogenic effects from furfuryl alcohol was conducted in mice (NTP,1999[7]). Therefore the test organism for the studies requested in this decision should also be mice. The exposure route should be oral and preferably by gavage to maximize the systemic exposure. Finally the tissues sampled and analysed in the comet assay shall be liver (this is a primary site of xenobiotic metabolism and is often highly exposed to both parent substance(s) and metabolite(s)), and kidney as it has been shown to be the target organ in the NTP study on carcinogenicity in mice. In addition, glandular stomach tissue shall be harvested and analysed as stomach is the first site of contact tissue after oral dosing and because the potential bioactivating enzyme sulfotransferase is abundant in GI tract tissues.

Therefore, pursuant to Article 46(1) of the REACH Regulation, the Registrant(s) is required to carry out the following study using the registered substance subject to this decision:

In Vivo Mammalian Alkaline Comet Assay (OECD test guideline 489) in mice, oral route, with examination of stomach, kidney and liver.

IV. Adequate identification of the composition of the tested material

In relation to the required experimental study, the sample of the substance to be used shall have a composition that is within the specifications of the substance composition that are given by all Registrant(s). It is the responsibility of all the Registrant(s) to agree on the tested material to be subjected to the test subject to this decision and to document the necessary information on composition of the test material. The substance identity information of the registered substance and of the sample tested must enable the evaluating MSCA and ECHA to confirm the relevance of the testing for the substance subject to substance evaluation. Finally, the test must be shared by the Registrant(s).

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[4] *Sachse B., Meinl W., Sommer, Y., Glatt, H., Seidel, A., Monien, B.H. 2014a,. Bioactivation of food genotoxicants 5-hydroxymethylfurfural and furfuryl alcohol by sulfotransferases from human, mouse and rat: a comparative study. Archives of Toxicology (early view: http://download.springer.com/static/pdf/311/art%253A10.1007%252Fs00204-014-1392-6.pdf?auth66=1416909069_ec7684a3e1c50f5ca135dcb7e95812a9&ext=.pdf*

[5] *Sachse, B., Meinl, W., Glatt, H., Monien, B.H. 2014b. The effect of knockout of sulfotransferases 1a1 and 1d1 and of transgenic human sulfotransferases 1A1/1A2 on the formation of DNA adducts from furfuryl alcohol in mouse models. Carcinogenesis 35 (10): 2339-2345.*

[6] *Kirkland D1, Speit G.2008.Evaluation of the ability of a battery of three in vitro genotoxicity tests to discriminate rodent carcinogens and non-carcinogens III. Appropriate follow-up testing in vivo. Mutat Res. 2008, 654: 114-32.*

[7] *NTP (1999). NTP Technical report on the toxicology and carcinogenesis of furfuryl alcohol (CAS No. 98-00-0) in F344/N rats and B6C3F1 mice (inhalation studies). NTP TR 482 NIH Publication No. 99-3972. Testing laboratory: Battelle Pacific Northwest Laboratories, Richland, WA, USA. Report no.: NIH Publication No. 99-3972. Owner company: U. S. Department of Health and Human Services, Public Health Service, National Institutes of Health. Report date: 1999-02-28.*

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

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

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

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

VI. Information on right to appeal

An appeal may be brought against this decision to the Board of Appeal of ECHA under Articles 52(2) and 51(8) of the REACH Regulation. Such an appeal shall be lodged within three months of receiving notification of this decision. Further information on the appeal procedure can be found on the ECHA's internet page at http://www.echa.europa.eu/regulations/appeals. The notice of appeal will be deemed to be filed only when the appeal fee has been paid.

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Director of Evaluation

Annex: List of registration numbers for the addressees of this decision. This annex is confidential and not included in the public version of this decision.