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European Chemicals Agency

Decision number: CCH-D-0000001554-76-04/F
Date for the decision: 1 July 2011

Helsinki, 1 July 2011

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

For BHT [redacted] CAS [redacted] (EC No. 485-290-0), 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 (the REACH Regulation).

I. Procedure

Pursuant to Article 41(1) of the REACH Regulation, ECHA has performed a compliance check of the registration dossier for **BHT [redacted] CAS [redacted] (EC No. 485-290-0)** submitted by [redacted] (the "Registrant"), latest submission [redacted] for [redacted]

The compliance check was initiated on 25 August 2010.

On 4 January 2011 ECHA notified the Registrant of its draft decision and invited him pursuant to Article 50(1) of the REACH Regulation to provide comments within 30 days of the receipt of the draft decision.

By 3 February 2011 the Registrant did not provide any comments on the draft decision to ECHA.

On 18 February 2011 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 to amend the draft decision within 30 days. Subsequently, Competent Authorities of the Member States submitted proposals for amendments to the draft decision.

On 23 March 2011 ECHA notified the Registrant of proposals for amendment to the draft decision and invited him pursuant to Article 51(5) of the REACH Regulation to provide comments within 30 days of the receipt of the notification.

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Thereafter, ECHA reviewed the proposals for amendments received and decided to amend the draft decision accordingly.

On 4 April 2011, the draft decision was referred to the Member State Committee.

On 19 April 2011, the Registrant provided comments on the proposed amendments.

The Member State Committee took the comments of the Registrant into account.

After discussion in the Member State Committee meeting on 25-27 May 2011, the Member State Committee modified the amended draft decision. On 26 May 2011 the Member State Committee reached unanimous agreement on the draft decision and ECHA has taken the decision accordingly pursuant to Article 51(6) of the REACH Regulation.

This decision does not imply that the information provided by the Registrant in his registration dossier is in compliance with the REACH requirements. The decision does not prevent ECHA to initiate a compliance check on the present dossier at a later stage.

II. Information required

1) Pursuant to Articles 41(1)(a), 41(3), 10(a)(vi) and (vii), [redacted] of the REACH Regulation, the Registrant shall submit the following information using the test method as indicated below:

- ***In vivo eye irritation*** (Annex VIII, 8.2.1. of the REACH Regulation; Method B.5 of Commission Regulation (EC) No 440/2008 (EU Method B.5.) is recommended)

- ***In vitro gene mutation study in mammalian cells*** (Annex VIII, 8.4.3. of the REACH Regulation; EU Method B.17 is recommended)

2) Pursuant to Articles 41(1)(c), 41(3), 10(b) and 14 as well as Annexes I and VI of the REACH Regulation, the Registrant shall provide the following chemical safety report (CSR) related information and update the CSR accordingly:

- ***Exposure assessment (consisting of the generation of exposure scenario(s) and exposure estimation) and a risk characterisation for workers during the maintenance operations of the assembly lines.***

- A ***full justification for the derivation of DNELs for workers*** (section 5.11 of the CSR) in order to demonstrate that the following factors have been taken into account:
  - the uncertainty arising, among other factors, from the variability in the experimental information and from intra- and inter-species variation;
  - the nature and severity of the effect;
  - the sensitivity of the human (sub-)population to which the quantitative and/or qualitative information on exposure applies; and
  - that the DNELs reflect the likely route(s), duration and frequency of exposure.

  If the current derivation is not fully justified, the Registrant should reconsider the present DNEL and reassess related risks.

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- ***Workers' dermal exposure assessment for the exposure situation "break down of the volume" should be refined in order to take into account any operational conditions and risk management measures. Personal protective equipment, such as gloves*** to be worn need to be specified clearly when handling the substance or mixture, including:
  - The type of glove material,
  - The breakthrough time of the glove material, with regard to the amount and duration of dermal exposure.

Pursuant to Article 41(4) of the REACH Regulation, the Registrant shall submit the information in the form of an updated IUCLID dossier to ECHA by **1 July 2012 - 12 months from the date of the decision.**

III. Statement of reasons

Based on the examination of the technical dossier, ECHA concludes that the information therein, submitted by the Registrant for registration of the above mentioned substance in accordance with Articles 6 and 7 of the REACH Regulation, does not comply with the requirements of Articles 10, 12, 13 and 14 and with Annexes I, VI and VIII thereof. Consequently, the Registrant is requested to submit the information mentioned above that is needed to bring the registration into compliance with the relevant information requirements.

1) Missing information related to endpoints

In vivo eye irritation

The technical dossier does not contain information for ***in vivo* eye irritation** as required by Annex VIII, 8.2.1. of the REACH Regulation. This information is waived by the Registrant who makes reference to Annex XI, 1.4. of the REACH Regulation and with the justification that an *in vitro* study (HET-CAM test) is already provided.

ECHA points out that an *in vivo* eye irritation is a standard requirement of Annex VIII, 8.2.1 [redacted] which may only be omitted when column 2 of Annex VIII, 8.2.1 or Annex XI so allows. These provisions do not allow the omission of the *in vivo* information on the basis that the Registrant has provided an *in vitro* study (HET-CAM test).

In relation to Annex XI, 1.4, ECHA notes that the registration dossier does not contain any classification for eye irritation. The results of the HET-CAM test indicate irritation scores that are just below the threshold for classification as "severe eye irritant" (irritation score is 7.5, max irritation score is 8.64. According to ICCVAM, severe irritancy classification applies when the irritation score exceeds 9). This implies that, contrary to Annex XI, 1.4 requirements, the results are not adequate for the purpose of classification and labelling and/or risk assessment and that the irritation potency of the registered substance should be investigated further.

The Registrant is therefore requested to perform an *in vivo* eye irritation study. The recommended test method is EU Method B.5.

In vitro gene mutation study in mammalian cells

The technical dossier does not contain information for ***in vitro* gene mutation study in mammalian cells,** as required by Annex VIII, 8.4.3. of the REACH Regulation. This

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information is waived by the Registrant. According to Annex VIII, 8.4.3. of the REACH Regulation, the *in vitro* gene mutation study in mammalian cells needs to be conducted if results are negative from both an *in vitro* gene mutation study in bacteria (Annex VII, 8.4.1.) and from an *in vitro* cytogenicity study in mammalian cells or an *in vitro* micronucleus study (Annex VIII, 8.4.2.). In the technical dossier provided by the Registrant the *in vitro* gene mutation study in bacteria is negative, and the *in vitro* cytogenicity study in mammalian cells (chromosome aberration test) is negative as well.

Therefore, ECHA concludes that the waiving proposed by the Registrant is not acceptable. In order to meet this information requirement, the Registrant is requested to perform an *in vitro* gene mutation study in mammalian cells. The recommended test method is EU Method B.17.

2) Missing information related to the Chemical Safety Report (CSR)

Exposure assessment and risk characterisation for workers during the maintenance operations of the assembly lines

ECHA states that exposure and risk assessments for workers during maintenance of the assembly lines are missing in the registration dossier. Pursuant to Article 14(4) and Annex I sections 0.6, 5 and 6 of the REACH Regulation, a registration for a substance produced in quantities of [redacted] which meets the criteria for classification as dangerous in accordance with Directive 67/548/EEC shall include for all identified uses an exposure assessment and a risk characterisation as part of the CSR. As from 1 December 2010 the above obligation applies if the substance is classified under any of the listed hazard classed in the amended Article 14(4) of the REACH Regulation.

ECHA notes that in the technical dossier and the chemical safety report the Registrant has classified the registered substance as dangerous in accordance with Directive 67/548/EEC criteria and described the manufacture and uses of this substance, including "*handling of tablets*" and "*break down of volume*". However, an exposure assessment and risk characterisation for workers during the maintenance operations of the assembly lines is missing.

The Registrant is therefore requested to add to the chemical safety report an **exposure assessment (consisting of the generation of exposure scenario(s) and exposure estimation) and a risk characterisation for the use of the registered substance by workers during maintenance of the assembly lines**. If relevant, risk management already in place should be taken into account.

Full justification for the derivation of DNELs for workers

Annex I, 1.4.1. of the REACH Regulation requires that the following factors shall, among others, be taken into account when deriving DNELs:

- the uncertainty arising, among other factors, from the variability in the experimental information and from intra- and inter-species variation;
- the nature and severity of the effect;
- the sensitivity of the human (sub-)population to which the quantitative and/or qualitative information on exposure applies.

Annex I, 1.4.1. also requires that a full justification for the establishment of DNELs is given specifying, among others, the choice of information used, the route of exposure and the duration and frequency of exposure of the substance.

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The ECHA "Guidance on information requirements and chemical safety assessment" (Volume 8, R8) provides further details and specifically provides default factors which should be applied to derive DNELs in the absence of substance specific information.

ECHA notes that in the CSR provided by the Registrant, the worker dermal DNEL is set as 0.3 mg/kg/day and the worker inhalation DNEL as 5 mg/m^3. The following assessment factors (AF) were applied by the Registrant:

For the dermal route:
- interspecies (rat): [redacted]
- intraspecies (workers): [redacted]
- exposure duration: [redacted]
- dose-response [redacted]

(overall AF [redacted]

For the inhalation route:
- interspecies (rat): [redacted]
- intraspecies (workers): [redacted]
- exposure duration: [redacted]
- dose-response: [redacted]

For the extrapolation of the results from the oral route to inhalation, the Registrant seems to have applied a correction factor of [redacted] in the calculation formula.

The ECHA Guidance (see above) recommends the application of the following default assessment factors[1]:

For the dermal route:
- interspecies (rat, correction for differences in metabolic rate per body weight): 4
- interspecies (remaining differences): 2.5
- intraspecies (workers): 5
- exposure duration (subacute to chronic or sub-chronic to chronic): 6 or 2
- dose-response (only LOAEL is available): a range from 3 to 10 (because of the severity of the effects observed, i.e. the substance being classified as Repr. Cat2; R61, an extrapolation factor of 10 should be considered)

(overall AF: 300 to 3000).

For the inhalation route:
- interspecies (rat, correction for differences in metabolic rate per body weight): none
- interspecies (remaining differences): 2.5
- intraspecies (workers): 5
- exposure duration (subacute to chronic or sub-chronic to chronic): 6 or 2
- dose-response (only LOAEL is available): a range from 3 to 10 (because of the severity of the effects observed, i.e. the substance being classified as Repr. Cat2; R61, an extrapolation factor of 10 should be considered)

(overall AF: 75 to 750).

For the extrapolation of the results from the oral route to inhalation the ECHA Guidance R.8 (section R.8.4.2 at page 25) recommends in the absence of substance specific information to take into account the potential difference in absorption by assuming, 50% oral absorption

[1] Link to ECHA guidance document R.8 is:
http://guidance.echa.europa.eu/docs/guidance_document/information_requirements_r8_en.pdf?vers=20_08_08

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and 100% for inhalation absorption resulting in a additional route to route correction factor of 0.5 in the calculation formula which would lower the calculated inhalation LOAEL by half.

ECHA observes that the Registrant did not follow recommendations of ECHA's Guidance R.8 and did not provide a full justification for the derivation of worker DNEL in line with Annex I, 1.4.1. Instead, he applied less protective assessment factors than those recommended by the ECHA guidance and did not apply assessment factors to cover uncertainties due to remaining interspecies differences (i.e. not related to allometric scaling), uncertainties due to difference in exposure duration between laboratory and real conditions, and uncertainties due to the lack of NOAEL. Full justification for this approach is missing in the registration dossier.

The worker dermal DNEL calculated according to the ECHA recommendations would then be between 3 and 30 µg/kg/day. In contrast, the DNEL calculated by the Registrant is 300 µg/kg/day, i.e. 100 to 10 fold higher. For inhalation, assuming that a worker inhales 10 m^3 per day, the worker inhalation DNEL calculated according to the ECHA recommendations would be between 0.012 and 0.120 mg/m^3 whereas in the registration dossier it is set as 5 mg/m^3. Worker exposure as provided in the registration dossier is arguably high, when compared to the DNELs calculated by the ECHA guidance. Currently, a potential risk for workers cannot be excluded.

Therefore, the Registrant is, in line with Annex I, 1.4.1, requested to **fully justify the DNEL derivation for workers** provided in the CSR by specifying

- the uncertainty arising, among other factors, from the variability in the experimental information and from intra- and inter-species variation;
- the nature and severity of the effect;
- the sensitivity of the human (sub-)population to which the quantitative and/or qualitative information on exposure applies;
- and that the DNELs reflect the likely route(s), duration and frequency of exposure.

If the current derivation is not fully justified, the Registrant should reconsider his DNELs and reassess related risks. The chemical safety report is requested to be amended accordingly.

Workers' dermal exposure assessment for the exposure situation "break down of the volume", taking into account any operational conditions and risk management measures

ECHA further notes that in pages 36-37 of the CSR, a risk characterisation ratio (RCR) above 1 [redacted] is reported for dermal exposure of workers (scenario: "*break down of volume*"). Article 14(6) as well as Annex I, 0.1 and 6.2 of the REACH Regulation require registrants to identify and apply appropriate measures to adequately control the risks identified in the CSR. The exposure shall be estimated and risks shall be characterised under the assumption that relevant risk management have been implemented.

The Registrant claims that this risks for dermal exposure for workers can be "*adequately controlled by wearing of gloves*" but **dermal exposure assessment taking into account operational conditions and risk management measures** (for instance, wearing of gloves) is missing in the dossier. Pursuant to Annex VI, section 5 of the REACH Regulation the information provided in the registration dossier must be consistent with that in the Safety Data Sheet. The requirements of Safety Data Sheets are specified in Annex II. According to section 8.2.1. (b) of Annex II the type of gloves to be worn needs to be specified clearly when handling the substance or mixture, including:

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- The type of material,
- The breakthrough time of the glove material, with regard to the amount and duration of dermal exposure.

Therefore, the Registrant is requested to provide these missing data and update the CSR accordingly.

IV. General requirements for the generation of information and Good Laboratory Practice

ECHA always reminds registrants of the requirements of Article 13(4) of the REACH Regulation that reads:

> *"Ecotoxicological and toxicological tests and analyses shall be carried out in compliance with the principles of good laboratory practice provided for in Directive 2004/10/EC or other international standards recognised as being equivalent by the Commission or the Agency and with the provisions of Directive 86/609/EEC, if applicable."*

According to Article 13(3) of the REACH Regulation, tests that are required to generate information on intrinsic properties of substances shall be conducted in accordance with the test methods laid down in a Commission Regulation or in accordance with other international test methods recognised by the Commission or the European Chemicals Agency as being appropriate. Thus, the registrant shall refer to Commission Regulation (EC) No 440/2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 adapted to technical progress and use the applicable test methods to generate the information on the endpoints indicated above.

National authorities monitoring good laboratory practice (GLP) maintain lists of test facilities indicating the relevant areas of expertise of each facility.

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.

Done at Helsinki,

[redacted]

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