European Chemicals Agency

Decision number: CCH-D-0000001697-64-04/F Helsinki, 20/10/2011
Decision date: 20 October 2011

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

For Aniline, CAS 62-53-3 (EC No 200-539-3), 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 the ECHA has performed a compliance check of the registration dossier for **Aniline, CAS 62-53-3 (EC No 200-539-3)** submitted by [redacted] (Registrant), latest submission number [redacted], for >1000 tonnes per year.

The compliance check was initiated on 8 April 2011.

On 31 May 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.

On 30 June 2011 the Registrant provided to ECHA comments on the draft decision.

ECHA reviewed the further information received and amended the draft decision accordingly.

On 29 July 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 did not propose amendments to the draft decision and ECHA took the decision pursuant to Article 51(3) of the REACH Regulation.

This compliance check decision does not prevent ECHA to initiate further compliance checks on the present dossier at a later stage.

II. Information required

1) Pursuant to Articles 41(1)(c), 14 and Annex I of the REACH Regulation the Registrant shall submit in the chemical safety report:

   a. An assessment of short-term exposures for workers and risk characterisation thereof;
   b. A DNEL based on the No Observed Effect Level of aniline for causing methaemoglobinaemia, or a justification for the choice of an effect level for basing the DNEL;
   c. A DNEL and risk characterisation for any relevant, vulnerable sub-population of people with an inherited disorder of glucose-6-phosphate dehydrogenase deficiency;
   d. Documentation that risks to workers are adequately controlled

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 **22 October 2012,** 12 months from the date of the decision.

At any time, the Registrant shall take into account that there may be an obligation to make every effort to agree on sharing of information and costs with other registrants.

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 for the purpose of registration within the applicable tonnage band of > 1000 tonnes per year in accordance with Article 6/7 and 11(2) of the REACH Regulation, does not comply with the requirements of Articles 10, 12 and 13 and/or with Annex I 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 Chemical Safety Report

Annex I sets out the general provisions for assessing substances and preparing chemical safety reports (CSR).

(a) An assessment of short-term exposures for workers and risk characterisation thereof

Annex I, section 5.2.4 of the REACH Regulation, requires the Registrant to perform an estimation of the exposure levels for all human populations (workers in this case) for which exposure to the substance is known or reasonably foreseeable. Such estimations shall take account of spatial and temporal variations in the exposure pattern, and in particular, duration and frequency of exposure according to the operational conditions, and the activities of workers related to the processes and the duration and frequency of their exposure to the substance. This is specified in the

REACH Guidance on Information Requirements and Chemical Safety Assessment (R.14.4.6), which states:

> "Exposure to some substances may lead to acute health effects. If a substance is classified for acute effects and 'peak exposure' is likely to occur, an acute DNEL should be derived (Chapter R.8). Exposure situations without 'peak exposure' (i.e. an acute exposure level clearly higher than the related full shift exposure level) are very rare. Therefore, in most cases a classification for acute effects should lead to an acute DNEL. In order to provide a relevant estimate of exposure the assessor should request acute exposure data. If such data are available they should be evaluated in the same way as described earlier. Where the data are of sufficient quality and reliability they can be used to provide a reasonable worst case and typical value for acute exposure. In the risk assessment the comparison should be made with a relevant DNEL, e.g. an acute DNEL."

The Registrant has derived short-term DNELs, but has not derived short-term exposure estimates or risk characterisation ratios. According to Annex I, these are required. There is therefore a lack of required information. The Registrant is accordingly requested to perform the appropriate exposure assessment and risk characterisation, and to update the CSR for this endpoint. The Registrant should be aware that a short-term exposure assessment and risk characterisation was performed in the EU Risk Assessment Report for aniline (hereafter the "EU RAR").

(b) A DNEL based on the No Observed Effect Level of aniline for causing methaemoglobinaemia, or a justification for the choice of an effect level for basing the DNEL

Annex I, section 1.4 of the REACH Regulation, requires the Registrant to establish derived no effect levels (DNEL(s)) for the registered substance. Specifically, it is required that:

> "A full justification shall be given specifying, inter alia, the choice of the information used, the route of exposure (oral, dermal, inhalation) and the duration and frequency of exposure to the substance for which the DNEL is valid."

In the dossier submitted, a full justification has not been provided for the use of an effect level (35 mg of aniline per person, which induces methaemoglobinaemia in humans), as opposed to a No Observed Effect Level, upon which to base the point of departure for DNEL derivation.

Additionally, Annex I, 0.5, provides as follows:

> "Where available and appropriate, an assessment carried out under Community legislation (e.g. risk assessments completed under Regulation (EEC) No 793/93) shall be taken into account in the development of, and reflected in, the chemical safety report. Deviations from such assessments shall be justified."

The EU RAR report for aniline uses the No Observed Effect Level, of 15 mg per person, upon which to base the risk assessment. In the dossier submitted, there is no justification for the deviation from this report.

The Registrant is accordingly requested to establish the appropriate DNEL based on an appropriate point of departure, and to update the CSR for this endpoint, or alternatively, to justify fully the use of an effect level that induces statistically-significant levels of methaemoglobinaemia in humans.

(c) A DNEL and risk characterisation for the vulnerable sub-population of people with an inherited disorder of glucose-6-phosphate dehydrogenase deficiency

Annex I, section 1.4 of the REACH Regulation, requires the Registrant to establish derived no effect levels (DNEL(s)) for the registered substance. Specifically, it is required that:

> "However, taking into account the available information and the exposure scenario(s) in Section 9 of the Chemical Safety Report it may be necessary to identify different DNELs for each relevant human population (e.g. workers, consumers and humans liable to exposure indirectly via the environment) and possibly for certain vulnerable sub-populations (e.g. children, pregnant women) and for different routes of exposure."

For the human health risk assessment, the Registrant has specifically identified a mechanism of action for the substance in inducing haemolytic anaemia, and this mechanism is central to the Registrant's risk assessment. It has been established that glucose-6-phosphate dehydrogenase deficiency confers enhanced sensitivity to drugs that cause haemolytic anaemia (reviewed in Blood [2008] 111: 16-24). The phenotype of glucose-6-phosphate dehydrogenase deficiency has been shown by genetic studies to be widespread (e.g. Science [2001] 293: 455-462). It can be concluded that there is a sub-population which is vulnerable to the toxicity of this substance, and the Registrant has not derived a DNEL or performed a risk characterisation for this group. Alternatively, the Registrants could obviate the need for deriving a DNEL in a sensitive sub-population if they could show that there were sufficient measures in place to identify vulnerable sub-populations. For example, if all workers undergo biomonitoring for methaemoglobinaemia, this would be able to detect sensitive individuals, allowing for such individuals to be removed from contact with the registered substance. The Registrant is accordingly requested to establish the appropriate DNEL for any relevant, vulnerable sub-population and to update the CSR for this endpoint.

(d) Documentation that risks to workers are adequately controlled

Article 14(6) as well as Annex I, 0.1, 5.2.4 and 6.2-6.4 of the REACH Regulation require registrants to identify and apply appropriate measures to adequately control the risks identified in CSR. The exposure shall be estimated and risks shall be characterised in the CSR under the assumption that relevant risk management measures have been implemented.

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 (amended by Commission Regulation (EC) No 453/2010). According to section 8.2.2.2(b) of Annex II, the type of gloves to be worn shall be clearly specified based on the hazard of the substance or mixture and potential for contact and with regard to the amount and duration of dermal exposure, including:

- The type of material and its thickness,
- The typical or minimum breakthrough times of the glove material

The Registrant is requested to provide documentation for the recommended material, thickness and breakthrough times for protective gloves, with regard to the amount and duration of dermal exposure in the CSR.

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 as adapted to to the 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]

Jukka Malm
Director of Regulatory Affairs