~~CONFIDENTIAL~~

European Chemicals Agency

Decision number: CCH-D-0000001556-72-06/F Helsinki, 7 November 2011

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

**For CCP-V-1, CAS [redacted] (EC Nr. 439-730-3), 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 (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 **CCP-V-1, CAS [redacted] (EC Nr. 439-730-3)** submitted by [redacted] (the "Registrant"), latest submission number [redacted], for 10 - 100 tonnes per year.

The compliance check was initiated on 21 June 2010.

On 4 January 2011 ECHA notified the Registrant of its draft decision and invited him to provide comments.

On 2 February 2011 the Registrant provided comments on the draft decision and an updated IUCLID file to ECHA. ECHA has considered the information received and amended the draft decision accordingly.

On 17 June 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 amendment to the draft decision.

On 20 July 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.

ECHA reviewed the proposals for amendment received and modified the draft decision accordingly.

On 1 August 2011, the draft decision was referred to the Member State Committee.

On 19 August 2011 the Registrant provided comments on the proposals for amendment. The Member State Committee took the comments of the Registrant into account.

After discussion in the Member State Committee meeting on 20-23 September 2011, the draft decision was further modified by the Member State Committee and a unanimous agreement of the Member State Committee on the modified draft decision was reached on 23 September 2011.

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

II. Information required

1) Pursuant to Articles 41(1)(a), 41(3), 10(a)(vii), 12(1)(c) and Annex VIII of the REACH Regulation the Registrant shall submit the information using the test method as indicated on

   - *In vitro* cytogenicity study in mammalian cells or *in vitro* micronucleus study for mutagenicity (Annex VIII, 8.4.2.; EU Method B.10 or OECD 487);
   - Combined short-term repeated dose toxicity study (28 days) and reproduction/developmental toxicity screening test in rat using the oral route of administration (Annex VIII, 8.6.1. and 8.7.1., OECD 422). ECHA further specifies that blood sampling shall only be performed at termination of the OECD 422 study.

2) Pursuant to Articles 41(1)(c), 41(3) and Annex I of the REACH Regulation the Registrant shall submit the information on:

   - Emission estimates resulting from the manufacture
   - Predicted environmental concentrations.

3) Pursuant to Articles 41(1)(c), 10(b), 14 and Annex I of the REACH Regulation the Registrant shall submit the following information in the form of an update Chemical Safety Report (CSR):

   - Revised PBT assessment.

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 **7 November 2012**.

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 Article 6 of the REACH Regulation, does not comply with the requirements of Articles 3, 10, 12 and 13 and with Annexes I, VII, 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**

Pursuant to Articles 10(a)(vii), 12(1)(c) and Annex VIII of the REACH Regulation, a registration for a substance produced in quantities of 10 – 100 tonnes per year shall contain as a minimum the information specified in Annex VIII of the REACH Regulation.

1.1) Mutagenicity

The technical dossier contained a data waiver for the following endpoint:

*In vitro* cytogenetics (Annex VIII, 8.4.2.)

The data waiver is applied on the basis that, in the study performed according to the OECD guideline 476 (*In vitro* mammalian cell gene mutation test), "gene mutations within the TK gene (11-13 kilobases) and chromosomal events involving the gene may be detected." According to ECHA Guidance, the OECD guideline study 476 is not recognised as an adequate test for cytogenetic aberrations: it may detect gross structural chromosome aberrations, but it is not stated that it can detect numerical chromosome aberration. ECHA notes that the Registrant, in their comments to the draft decision, provided scientific papers and other evidence to support the acceptability of this test. These papers antedate the relevant ECHA guidance, and the relevant existing scientific information was considered in reaching the conclusions of the ECHA guidance. Consequently, these do not provide a novel basis for over-riding the ECHA guidance. Additionally, the Registrant has argued that the test is acceptable in other regulatory testing regimes, specifically citing ICH, the FDA and specific EU member states. ECHA notes that the regulatory testing requirements for genotoxicity under REACH are distinct from those in other legislations, and that consequently, acceptability of a test under other legislative frameworks does not necessarily guarantee the acceptability of a test within the context of the REACH Regulation. Moreover, the scientific papers provided by the Registrant do not satisfactorily address the issue of whether the colony sizing information by itself in the OECD 476 assay is a full and sufficient assay for detection of chromosome aberration. This test therefore cannot be accepted as a test that fulfils the information requirement of Annex VIII, 8.4.2. The "waiver" fails to meet the conditions in column 2 of Annex VIII, 8.4.2., or the conditions of Annex XI, and so the waiver cannot be accepted. The Registrant is accordingly requested to submit the information for this endpoint using the test method EU B.10 or OECD 487 performed with the registered substance.

1.2) Repeated dose toxicity and screening for reproductive/developmental toxicity

There are information deficiencies for these two endpoints for the following reasons:

A) Short term repeated dose toxicity (Annex VIII, 8.6.1.)

The technical dossier contained the results of a repeated dose toxicity 28-days study in rat by oral gavage (OECD 407). Pursuant to Annex VIII, 8.6.1. Column 2 further studies may be required by the Agency in accordance with Article 40 or 41 of the REACH Regulation in case of toxicity of particular concern (*e.g.* serious/severe effects). Given that toxicity of particular concern (i.e. death) had been shown at both high and mid-dose, the condition of Annex VIII, 8.6.1., Column 2 for requesting further studies is met. It is necessary to further examine the toxicity of the registered substance at sub-lethal doses in order to provide information on repeated-dose toxicity which is adequate for the purposes of Classification and Labelling, and also for robust risk management.

B) Toxicity for reproduction screening test (Annex VIII, 8.7.1.)

The Registrant has omitted this endpoint based on absence of relevant human exposure as provided for in Annex XI, 3.2.

The justification for waiving fails to meet the specific clauses set out in Annex XI, 3.2(a). The Registrant has claimed that all three conditions in section 3.2(a) are met, but has failed to demonstrate this:

First, the results of the exposure assessment covering all relevant exposures throughout the life cycle of the substance does not demonstrate the absence of, or no significant exposure, in all scenarios of the manufacture. Therefore, the dossier is incompliant with Annex XI, 3.2(a)(i).

Second, no specific DNEL for reproductive toxicity has been derived. The endpoint of repeated dose toxicity has been used to derive the lowest DNEL. The resulting DNEL and risk characterization do not take full account of the increased uncertainty resulting from the omission of the information requirement for reproductive toxicity. The dossier is therefore incompliant with Annex XI, 3.2(a)(ii).

Third, the comparison of the derived DNEL with the results of the exposure assessment does not show that exposure are always well below the derived DNEL. The dossier is therefore incompliant with Annex XI, 3.2(a)(iii).

Given that there is no justification for the adaptation of the standard testing regime, there is a data gap for Annex VIII, 8.7.1.
It follows that the Registrant has information deficiencies for the information requirements of Annex VIII, 8.6.1. and 8.7.1., and the Registrant is therefore obliged to fulfil these information requirements. A combined repeated dose toxicity test with the reproduction/developmental toxicity screening test, as described in OECD method 422, satisfies the information requirements of both Annex VIII, 8.6.1. and Annex VIII, 8.7.1. The Registrant is accordingly requested to submit the information for these two endpoints using the test method: combined repeated dose toxicity test with the reproduction/developmental toxicity screening test in the rat by oral route (OECD method 422). As a result of discussions on the properties of the substance and on

animal welfare considerations, it was specified that blood sampling shall only be performed at termination of the OECD 422 study. The Registrant is requested to update the technical dossier and the CSR with the relevant information.

**2) Missing information related to the CSR**

Pursuant to Articles 41(1)(a), 41(3), 14(1), (3) and (4) as well as Annex I of the REACH Regulation, a Chemical Safety Report shall be provided including several steps. Annex I sets out the general provisions for assessing substances and preparing a CSR.

2.1) Emission estimates resulting from the manufacture of the registered substance

Annex I, 5.2.1. and 5.2.2. of the REACH Regulation requires the registrant to provide emission estimates in the exposure estimation during all relevant parts of the life-cycle of the substance resulting from the manufacture and each of the identified uses. Annex I 5.2.4 of the REACH Regulation requires that estimation of the exposure levels shall be performed for all environmental spheres for which exposure to the substance is known or foreseeable and shall take account among others of the duration and frequency of exposure according to the operational conditions.
The CSR does not contain the emission estimates during manufacture of the registered substance, only a qualitative assessment is provided. The Registrant is therefore requested to provide those emission estimates and update the CSR accordingly.

2.2) Predicted environmental concentrations

Annex I, 6.3. of the REACH Regulation requires the registrant to perform a risk characterization which consists of the comparison of the predicted environmental concentrations (PECs) in each environmental sphere with the PNECs. In the CSR no PECs for any of the environmental sphere are provided. The Registrant is therefore requested to provide the PECs in each environmental sphere and update the CSR accordingly.

**3) PBT assessment**

Pursuant to Article 14(3)(d) and Annex I, 4.1 of the REACH Regulation, a chemical safety assessment of a substance shall include a persistent, bioaccumulative and toxic (PBT) and very persistent and very bioaccumulative (vPvB) assessment.
Under the PBT assessment in the CSR, the Registrant has concluded that persistency of the substance cannot be excluded.
The Registrant has also concluded that the substance has no potential for bioaccumulation based on an OECD Guideline 305 flow-through fish bioaccumulation test. In this study, two concentrations were tested above the water solubility of the substance which is estimated with some uncertainty due to technical difficulties. The use of a dispersant is reported. ECHA considers that the test substance may not have been completely dissolved and therefore the calculated BCF values are uncertain. Moreover, ECHA is of the opinion that, based on the physico-chemical properties of the substance, a steady exposure concentration in the tests vessels would have been difficult to achieve even by using a flow-through design. Also, it could be anticipated

that uptake from the food will exceed uptake from water and therefore the biomagnification factor (BMF) derived from a dietary exposure bioaccumulation fish test is considered more relevant than a bioconcentration factor (BCF). Based on the above and on screening evidence by the use of non test information, ECHA considers that the study cannot be used alone to conclude on the bioaccumulation potential of the substance.
Moreover, the Registrant has concluded that the substance is not toxic based on acute aquatic tests. There are no chronic aquatic tests reported and, at present, the substance is not classified for human health. According to ECHA Guidance R11.1.3.3., for certain lipophilic substances (with a log Kow >5) acute toxicity may not occur at the limit of the water solubility of the substance tested (or the highest concentration tested). In such situations, chronic toxicity with a NOEC < 0.01 mg/l cannot be excluded, as these substances may not have had sufficient time in the acute test to be significantly taken up by the test organisms and to reach equilibrium partitioning.
ECHA takes the view that the acute aquatic tests alone cannot be used to conclude on the T criterium.
In summary, based on the above information, ECHA considers the substance may meet the screening criteria for PBT/vPvB. Consequently, the Registrant is requested to reassess the PBT properties of the registered substance and to update the CSR accordingly.
Pursuant to Annex I, 4.1, as the registration is at Annex VIII, the Registrant shall consider the information relevant for screening for P, B and T properties to decide whether further information needs to be generated for the PBT and vPvB assessment. If testing in accordance with Annex IX or X of the REACH Regulation is deemed necessary, the Registrant is required to submit a testing proposal.

## 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 1907/2008 as 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]

Jukka Malm
Director of Regulatory Affairs