MINISTERIUM
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LEBENSWERTES
ÖSTERREICH

SUBSTANCE EVALUATION

CONCLUSION DOCUMENT

as required by REACH Article 48

for

Succinic anhydride

EC No 203-570-0

CAS No 108-30-5

Evaluating Member State(s): Austria

Dated: 12.01.2015

Evaluating Member State Competent Authority

Austrian Federal Ministry of Agriculture, Forestry, Environment and Water Management

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Year of evaluation in CoRAP: 2013

Before concluding the substance evaluation a draft decision to request further information was issued on: April 2014

In order to close data requests the registrants submitted further information and study results. For those information/data no further testing was needed.

A revised registration dossier including requested amendments has been submitted; no further information is required at present.

Please find (search for) further information on registered substances here:

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work.

In order to ensure a harmonised approach, ECHA in cooperation with the Member States developed risk-based criteria for prioritising substances for substance evaluation. The list of substances subject to evaluation, the Community rolling action plan (CoRAP), is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by the Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. In this conclusion document, the evaluating Member State shall consider how the information on the substance can be used for the purposes of identification of substances of very high concern (SVHC), restriction and/or classification and labelling. With this Conclusion document the substance evaluation process is finished and the Commission, the registrants of the substance and the competent authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

DISCLAIMER

The Conclusion document has been prepared by the evaluating Member State as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006. The information and views set out in this document are those of the author and do not necessarily reflect the position or opinion of the European Chemicals Agency or other Member States. The Agency does not guarantee the accuracy of the information included in the document. Neither the Agency nor the evaluating Member State nor any person acting on either of their behalves may be held liable for the use which may be made of the information contained therein. Statements made or information contained in the document are without prejudice to any further regulatory work that the Agency or Member States may initiate at a later stage.

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1. CONCERN(S) SUBJECT TO EVALUATION

Succinic anhydride was originally selected for substance evaluation in order to clarify suspected risks about:

- Human health/Suspected CMR
- Human health/Sensitiser
- Exposure/High RCR

During the evaluation, another concern was identified. The additional concern was:

- Human health/Skin irritation/corrosion

The substance evaluation was targeted to all sections of the chemical safety assessment given in the IUCLID dossiers and chemical safety reports.

2. CONCLUSION OF SUBSTANCE EVALUATION

The following risks/concerns have been concluded in the scope of substance evaluation:

Suspected CMR

For reproductive toxicity (fertility and development) read across to maleic anhydride has been applied with the exemption of supportive intraperitoneal screening tests (Fabro S. et al., 1982, Fabro S. et al., 1976, Brown N.A et al., 1978).

The screening tests are not guideline and GLP conform and the test substance has been applied intraperitoneally. The application route is regarded as inappropriate for the intented uses (worker exposure: inhalation or dermal route). Beside the fact that the studies have some drawbacks, it has been shown that succinic anhydride only induces a significant incidence of malformations at doses within the adult lethality range (relative teratogenicity index is close to 1) (Fabro et al., 1982).

Due to lack of reproductive toxicity studies (REACH, Annex X) with succinic anhydride, a read across approach has been applied to fill the data gaps (REACH, Annex XI). The approach has been described only very briefly in the previous versions of the registrations. In a subsequent dossier update the registrants provided further justification for the read across approach, which allowed the evaluating Member State to conclude the evaluation.

In the read across approach a data matrix of relevant substances (maleic anhydride, succinic anhydride and their hydrolysis products - maleic acid, succinic acid) is provided. In the present form of the IUCLID dossier an attachment is provided, which illustrates the proposed read across approach carried out according to the REACH guidance[2].

Besides, the demonstration of the structural similarity to maleic anhydride, also the physicochemical parameters are given. The toxicological patterns of maleic anhydride and succinic anhydride are identical; both have sensitising as well as corrosive properties and hydrolyse rapidly under aqueous condition. The proposed read across approach to maleic anhydride is regarded as justified.

[2] ECHA (2008). Guidance on information requirements and chemical safety assessment chapter R.6: QSARs and grouping of chemicals.
(link: http://echa.europa.eu/documents/10162/13632/information_requirements_r6_en.pdf)

The two generation toxicity study comparable to OECD TG 416 (Two-generation reproduction toxicity study) carried out with the source substance maleic anhydride (Short et al., 1986) does not give evidence that maleic anhydride has negative effects on the reproductive system (fertility and development) and does not trigger classification.

Furthermore, succinic anhydride is rapidly hydrolysed to succinic acid. Succinic acid is present ubiquitous in mammalian cells. It is part of the Citrate Cycle. The body of evidence described in the supplementary document that succinic acid does not possess adverse effects on the reproductive system is plausible and valid. Furthermore, there is no evidence in the literature that anhydrides elicit adverse effects on the reproductive system (Kim et al., 2009).

The evaluating Member State concludes that there is sufficient information provided to determine the hazard profile of succinic anhydride in respect to developmental toxicity. The provided read across approach by the registrants together with supplementary teratogenicity studies and the complementary information on the hydrolysis product is regarded as sufficient to conclude that reproductive system is not a target organ of succinic anhydride.

Sensitiser

Results of the local lymph node assay (LLNA) demonstrate the skin sensitising properties of succinic anhydride. Although the LLNA test was developed and validated for identification of contact allergens, there is evidence that respiratory allergens will also elicit positive responses in this assay (Kimber, 1995). In addition, there is a growing body of evidence that effective sensitisation of the respiratory tract by chemicals defined as respiratory allergens can and does occur in response to dermal contact (Kimber et al., 2002).

Furthermore, based on comparison of data with other anhydrides (especially with the most similar anhydride form: maleic anhydride) respiratory sensitisation can be supposed, since anhydride structure is an alert for sensitisation properties. Anhydrides have the potential to react with the N-terminal amino acid to bind covalent to proteins.

The registrant(s) has self-classified succinic anhydride as Skin Sens. 1 and Resp. Sens. 1 accordingly. The evaluating Member State agrees on the classification and proposes a harmonised classification for these endpoints according to Regulation (EC) No 1272/2008.

Besides, the evaluating Member State considered the conduction of a qualitative risk assessment as necessary, since no DNELs can be derived for the sensitisation properties. A qualitative assessment has thereafter been carried out by the registrant(s) and has been accepted by the evaluating Member State.

Skin irritation/corrosion

For the endpoint skin irritation/skin corrosion further information during the assessment was requested by the evaluating Member State, since:

- Transformation step from the anhydride to its corresponding acid is a step in which exposed cellular structures (e.g., skin, eye) can be damaged. Hydrolysis of anhydrides is a critical step, which might possess irritating potential.
- Cyclic anhydrides (structural analogues to succinic anhydrides) possess moderate to severe skin irritation potential (Kim et al., 2009). Therefore a skin irritation effect of succinic anhydride cannot be excluded by read across to the hydrolysis product succinic acid.
- The most similar structural analogue maleic anhydride (CAS No 108-31-6, EC No 203-571-6) has harmonized classification as Skin Corr. 1B (Regulation (EC) No 1272/2008, Table 3.1).
- The acute dermal toxicity study indicates transient irritation potential of succinic anhydride.

Based on these considerations testing according to the recently acknowledged integrated approach on testing and assessment (IATA) for skin corrosion and irritation (OECD, 2014) was proposed via a draft decision by the evaluating Member State. As stated in IATA, a top down approach (test strategy: *in vitro* skin corrosion test followed by an *in vitro* skin irritation test in case the chemical is identified as not being corrosive) was needed to be carried out.

The registrants submitted two tests to determine the skin irritation/corrosion potential. An *in vitro* study skin corrosion test (OECD TG 431: Human skin model test), which demonstrated skin corrosive potential (Experimental study 1, 2014) and an *in vitro* skin irritation test (OECD 439: Reconstructed human epidermis (RHE) test method), which was negative with the applied test system (Experimental study 2, 2014).

These contradicting results can be explained by different exposure times of the applied test systems. As explicitly stated in IATA corrosive substances can therefore be detected as non-irritating substances in the irritating test systems but need to be considered as corrosive substances (OECD, 2014).

Based on the available data, the evaluating Member State concludes that succinic anhydride possess skin corrosion properties and needs to be classified accordingly.

Exposure

Referring to the hazard assessment, succinic anhydride is considered to be a skin and respiratory sensitizer and to cause harm to the skin. As it has not been possible to derive quantitative hazard reference values and to derive a threshold for the corresponding endpoints, a qualitative exposure and risk assessment was performed for demonstrating safe use by the registrants. The goal of the envisaged qualitative approach is to keep exposure to the substance as low as feasible and at irrelevant levels leading to no effects.

The industrial manufacture processes using/producing succinic anhydride are performed in closed, semi-closed systems. Nevertheless, some potential for inhalation and dermal exposure may still arise due to these ”contained” processes (PROC 1, 2, 3, 4) and due to required tasks like transfer of chemicals (PROC 8b), maintenance, etc. Therefore, local exhaust ventilation and engineering controls are applied in addition, if the used systems are considered to be not fully closed and release and exposure are considered to be possible. Workers involved in the production, handling, sampling and transfer of materials are trained in these procedures and the use of eye goggles, plastic gloves (no specific requirements but for example neoprene and coated neoprene /rubber / nitrile rubber gloves) and clothing with long sleeves and long legs, is required in order to minimise exposure. If inhalation exposure to succinic anhydride dust is considered to be possible, full face respirators are applied by the workers.

Based on the received data and descriptions provided by the registrants, the qualitative approach for the exposure and risk assessment was accepted. Referring to the explanations of the registrants, efficient RMM, PPE and RPE are used, if potential for exposure is possible. The degree and likeliness of human exposure is kept low during all processes. The currently applied measures are considered to be applicable for ensuring safe use and protecting workers. The covered industrial uses are considered to reveal an acceptable risk.

The available information on the substance and the evaluation conducted has led the evaluating Member State to the following conclusions, as summarised in the table below.

Conclusions	**Tick box**
Need for follow up regulatory action at EU level	x
Need for Harmonised classification and labelling	x
Need for Identification as SVHC (authorisation)	
Need for Restrictions	
Need for other Community-wide measures	
No need for regulatory follow-up action	

3. JUSTIFICATION FOR THE CONCLUSION ON THE NEED OF REGULATORY RISK MANAGEMENT

3.1. NEED FOR FOLLOW UP REGULATORY ACTION AT EU LEVEL

3.1.1. Need for harmonised classification and labelling

According to Article 36(1) of the Regulation (EC) No 1272/2008 substances that fulfil the criteria for respiratory sensitization category 1 (Resp. Sens. 1) (Annex I, section 3.4) shall be subject to harmonised classification. Therefore, the current harmonised classification of succinic anhydride needs to be amended.

The submitted hazard data also demonstrate that succinic anhydride possesses skin sensitisation properties and therefore a harmonised classification for Skin Sens. 1 is also proposed. Furthermore, the hazard data provided in the registration dossier by the lead registrant (full registration, joint submission) indicate that succinic anhydride should be classified as Eye Dam. 1 instead of Eye Irrit. 2. Test results of skin corrosion/irritation tests demonstrate that succinic anhydride needs a further classification for its skin corrosive properties, i.e. Skin Corr. 1B. The current Annex VI entry for succinic anhydride includes also Acute Tox 4* as a minimum classification as indicated by the reference * in table 3.1. Evaluation of experimental data of acute oral toxicity data reveals that the indication of the minimum classification (*) is not necessary.

In the C&L inventory differences in self-classification between notifiers have been discovered and the new interpretations of the data and changes in the Regulation (EC) NO 1272/2008 criteria need to be reflected in the harmonised classification.

Based on thorough evaluation of available hazard data an extension and revision of the current harmonised classification is proposed.

3.1.2. Need for Identification as a substance of very high concern, SVHC (first step towards authorisation)

No need for identification as a substance of very high concern, SVHC.

3.1.3. Need for restrictions

No need for restriction.

3.1.4. Proposal for other Community-wide regulatory risk management measures

No need for other Community-wide regulatory risk management measures.

3.2. NO FOLLOW-UP ACTION NEEDED

A follow-up action is proposed according to Article 48 of the REACH Regulation (for the purposes of Article 59(3)) (see Chapter 3.1.).

4. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

Need for harmonised classification and labelling has been identified during substance evaluation.

Follow-up action	Date for intention	Actor
Harmonised classification and labelling, Dossier Preparation	December 2014	Austria

5. References

Brown, N. A. et al (1978). The relationship between acylating ability and teratogenicity of selected anhydrides and imides. Toxicology and applied pharmacology, Vol.45 p.361, 1978.

Experimental study 1 (2014). In vitro skin corrosion test with succinic anhydride using a human skin model.

Experimental study 2 (2014). In vitro skin irritation test with succinic anhydride using a human skin model.

Fabro, S. et al (1976). Further studies on the mechanism of teratogenic action of thalidomide. The Pharmacologist, V 18.

Fabro S, Schull G, and Brown NA (1982). The relative teratogenic index and teratogenic potency: Proposed components of developmental toxicity risk assessment. Teratogenesis, Carcinogenesis, and Mutagenesis 2: 61-76 (1982).

Kim, J. H., Gibb, H. J., Iannucci, A (2009). Concise International Chemical Assessment Document 75. Cyclic acid anhydrides: Human Health Aspects, World Health Organisation (WHO)

Kimber I. 1995. Contact and respiratory sensitization by chemical allergens: uneasy relationships. Am. J. Contact Derm. 6, 34

Kimber I and Dearman RJ. 2002. Chemical respiratory allergy: role of IgE antibody and relevance of route of exposure. Toxicology 181-182, 311-315.

OECD, 2014. New guidance document on an integrated approach on testing and assessment (IATA) for skin corrosion and irritation. Series on Testing and Assessment No. 203. ENV/JM/MONO(2014)/19

Short RD, Johannsen FR, Levinskas GJ, Rodwell DE, and Schardein JL. (1986). Teratology and multigeneration reproduction studies with maleic anhydride in rats. Fundamental and Applied Toxicology 7: 359-66 (1986).