lebensministerium.at

SUBSTANCE EVALUATION

CONCLUSION DOCUMENT

as required by REACH Article 48

for

Maleic anhydride

EC No 203-571-6

CAS No 108-31-6

Evaluating Member State: Austria

Dated: 20 July 2014

Evaluating Member State Competent Authority

Assessor:

Umweltbundesamt GmbH, Spittelauer Lände 5, A-1090 Vienna

on behalf of the Austrian Competent Authority

Austrian Federal Ministry of Agriculture, Forestry, Environment and Water Management, Stubenring 1, 1010 Vienna, Austria

Contact:

Max Kinzl, Dr.

Department: Chemicals & Biocides
T: +43-(0)1-313 04/5655
F: +43-(0)1-313 04/5660
Stoffbewertung@umweltbundesamt.at

Umweltbundesamt GmbH
Spittelauer Lände 5
1090 Wien
Österreich/Austria

Year of evaluation in CoRAP: 2013

Member State concluded the evaluation without the need to ask further information from the registrants under Article 46(1) decision.

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

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

DISCLAIMER

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

CONTENTS

1. CONCERNS SUBJECT TO EVALUATION

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

- Human health/Sensitiser;
- Exposure/High RCR;
- Aggregated tonnage

During the evaluation no further concerns to be clarified under substance evaluation process were identified. Substance evaluation was targeted to all areas of risk assessment.

Maleic anhydride was proposed for substance evaluation based on Article 45(5) of the REACH Regulation. The evaluation was targeted to all sections of the chemical safety assessment given in the IUCLID dossiers and chemical safety reports of the registrants. Following main concerns were identified before and during Substance Evaluation by the evaluating member state.

The following grounds for concern refer to the former version of the registration dossiers submitted to ECHA before start of substance evaluation. As available data provided by the registrants during substance evaluation were considered to be sufficient for clarifying identified concerns and drawing conclusions, no new data/tests were considered to be required. The registration dossiers were updated during the first year of evaluation (current version). Some of the following concerns were targeted and clarified in the current registration dossiers, whereas some sections were not amended and contain these concerns, although data are available for clarification.

- Maleic anhydride is used as an intermediate for the preparation of other chemicals. Human exposure is limited to workers at industrial sites. Based on the information on the intended uses given in the registration dossiers, it was assumed that there is a potential for the existence of processes/tasks, where maleic anhydride is used in ways that higher exposure levels may occur, which might result in unacceptable risk referring to the hazard of maleic anhydride.
- Maleic anhydride is known to be a skin and respiratory sensitizer, the derived no effect levels proposed by the registrants were evaluated carefully, since it was not clear, if the sensitizing effects of the substance are covered by the proposed hazard reference values.

  Following DNELs were derived for workers and used for risk assessment in the former version of the registration dossier by the registrants.

DNEL long term, inhalation, local & systemic: 0,41 mg/m^3 The DNEL long term, inhalation, local was based on the German MAK value (MAK Maximale Arbeitsplatz Konzentration) which was derived from a 6 months inhalation study in rats, hamsters and rhesus monkeys. General systemic toxic effects can be expected to be covered by this DNEL. Two case reports of occupational respiratory sensitisation with unclear exposure (maleic anhydride as well as phthalic anhydrate) lead the MAK commission to review their MAK value, however, they concluded not to change it. The MAK commission stated, however, that there exists no reliable quantitative information on maleic anhydride concentrations which can be related to sensitisation or elicitation. Therefore, the sensitising effects of maleic anhydride were not covered by this

DNEL. Furthermore, the applied assessment factors (AFs) in the registration data were not in line with the REACH guidance. If AFs are reduced from the default this has to be justified adequately. The justification was missing.

DNEL acute, inhalation, local & systemic: 0,8 mg/m^3

Maleic anhydride is classified in category I by the MAK commission. This allows applying a factor of 2 for acute peak exposures. However, it is not guaranteed that this value is protective against respiratory sensitisation.

DNEL long term, dermal, local & systemic: 40µg/cm^2

The registrants stated based on the corrosivity, and skin & respiratory sensitising properties (it is stated that dermal contact may also induce respiratory sensitisation) of maleic anhydride dermal contact has to be excluded completely. This recommendation would be in line with the REACH guidance on CSA & IR. The registrantd stated that this is, however, hard to achieve – therefore the DNEL of 40µg/cm^2 is used to cover local & systemic as well as acute & chronic dermal effects. This value is derived from an EC_3 value from a LLNA. The information presented in the registration dossiers was insufficient to conclude whether this value was derived correctly. An EC_3 value can be regarded as a LOAEL value. The REACH guidance on CSA & IR chapter R.8 recommends to apply several AFs (vehicle or matrix effects: 1-10, occasionally higher; exposure conditions: 1-10, occasionally higher; interspecies difference: 1-10, occasionally higher) in order to derive DNELs from EC_3 values. Not a single assessment factor (AF) was applied to derive this DNEL, and no justification was provided. It also had to be checked whether the available human data (including information from workplace as well as patch tests) might result in a different value.

The registrant applied the DNELs mentioned above in the former quantitative risk assessment for deriving RCRs. The exposure assessment was not detailed and particular risk management measures (RMM) and personal protective equipment (PPE) not considered or not indicated to be required, as the resulting RCRs of these calculation were already below 1 (though quite close to 1 in some cases). The registrants concluded that the conditions applied for exposure estimation targeting RMMs and PPEs were sufficient to guarantee safe use conditions. However, as the DNELs mentioned above do not consider the sensitizing properties of maleic anhydride, this quantitative approach was considered to be not applicable and to be a concern revealing potential risk for human health.

- Available studies regarding the endpoints carcinogenicity and reprotoxicity were assessed by the evaluating member state for verifying, if the studies used by the registrants are sufficient and valid to determine the hazard. One rat carcinogenicity study is available, which has several deficiencies. Furthermore, the reprotoxicity studies were evaluated carefully. The description and data provided in the former CSRs and in the registration dossiers were insufficient to evaluate the available studies and to draw conclusions.

- For the exposure scenarios ECETOC TRA was applied for estimating quantitatively the exposure of workers. The substance was characterized as solid particles revealing a low dustiness (inhalative exposure to particles) for all of the

calculations. Based on these parameters only, inhalation exposure was estimated to be comparatively low and no LEV was required referring to the calculations and the corresponding RCRs (all RCRs were below 1). As the pure substance has a high volatility at room temperature (33 Pa at 25°C) and some uses are performed even at elevated temperatures above the melting point of the substance (substance is liquid and not solid), gaseous releases of the substance (even at room temperature) have to be taken into account in addition to potential exposure to particles in air. Therefore, a higher degree of risk management measures than recommended in the exposure scenarios was expected to be required (closed systems, LEV, etc.). From the description of the exposure scenarios it was not clear whether LEV is mandatory or not: LEV was only recommended and not stipulated and the required efficiency was not identified. The calculations were performed without the consideration of LEV. Omission of LEV seemed to be acceptable regarding the derived DNELs, as demonstrated in the risk assessment (RCRs below 1). However, as discussed in the section on hazard (see above) it was not conclusive whether sensitization was covered by this approach. The omission of LEV or closed systems appeared not to be acceptable at the workplace. (Besides, there were concerns that the contribution of gaseous releases were not covered within the calculations and that these uses/ESs require higher degrees of RMM than assumed for the exposure assessment, see comment above).

- Different efficiencies for gloves were indicated for different PROCs depending on the degree and amount of expected exposure (quantitative exposure assessment). As discussed in the hazard section it was doubted that the applied DNELs cover the sensitizing effects of maleic anhydride. Therefore, it is not conclusive to use gloves with lower efficiencies based on the risk assessment using the DNELs.

2. CONCLUSION OF SUBSTANCE EVALUATION

Submitted data were considered to be sufficient for chemical safety assessment and covering relevant topics of concern, no new data/tests related to hazard and exposure were considered to be required by the evaluating member state. Therefore, substance evaluation was finalised after the first year of evaluation.

Assessment of concerns subject to evaluation: human health

Appropriate tests for acute toxicity to determine the acute toxicity potential are available. Presented data confirm the harmonised classification of maleic anhydride as Acute Tox. category 4 (H302: harmful if swallowed) according to regulation (EC) No 1272/2008. The evaluating MS agrees with the registrant's evaluation of the acute toxicity data and harmonised classification of maleic anhydride as Acute Tox. category 4 (H302: harmful if swallowed).

Appropriate tests on skin and eye irritation/corrosion are available. Submitted experimental animal data support the harmonised classification of maleic anhydride as Skin Corr. 1B (H314: causes severe skin burns and eye damage). Corrosive substances may be toxic after inhalation, if maleic anhydride is inhaled, a hazard to the respiratory tract exists, and therefore maleic anhydride has to be supplementary labelled with EUH071 (corrosive to the respiratory tract). Results of eye corrosion test demonstrate that application of maleic anhydride to rabbit's eye has severe adverse effects. Based on these study reports the substance has to be classified according to criteria laid down in

Regulation (EC) No 1272/2008 as serious Eye damage category 1 (H 318: causes serious eye damage). The additional classification and labelling has already been covered by the self-classification of the registrants.

Sufficient data are available to identify and characterize the skin and respiratory sensitization hazard. The data substantiate the harmonised classification of maleic anhydride as Resp. Sens. category 1 (H334: May cause allergy or asthma symptoms or breathing difficulties if inhaled). For the skin sensitisation endpoint a sub-classification according to the CLP criteria as Skin Sens. category 1A (H317: May cause an allergic skin reaction) is warranted.

The repeated dose toxicity study carried out with rats demonstrates that maleic anhydride warrants a classification as STOT RE category 2 (oral) (H373: may cause damage to kidney through prolonged or repeated exposure). The LOAEL (males) in one oral toxicity study carried out with rats is 100 mg/kg bw based on renal changes (Humiston et al., 1975). Renal kidney changes have been also observed in the developmental toxicity study (Monsanto Company, 1982, Short et al., 1981). The evaluating member state proposes a harmonized classification. Furthermore, the outcome of inhalative repeated dose toxicity study (Goldenthal et al., 1979) warrant a classification according to criteria laid down in the regulation No 1272/2008 as STOT RE category 1 (H372: causes damage to respiratory system through prolonged or repeated exposure by inhalation).

Sufficient data to determine the mutagenic potential have been presented by the registrants. Besides information from in *in vitro* studies a valid guideline comparable *in vivo* study has been submitted (Confidential, 1983). Sprague Dawley albino rats were exposed to target concentrations of 0, 1, 100 mg/m^3 for six hours. No treatment related effects have been observed. The lack of significant mutagenic potential is in accordance with the outcome of the carcinogenicity study.

Original study to evaluate the carcinogenic potential of maleic anhydride has been provided by the registrants upon request. The study is comparable to the test guideline OECD 451 and the study is reliable with restrictions (Klimisch score 2). The carcinogenic potential of maleic anhydride has been studied in a two-year oral feeding guideline comparable study carried out with rats (Procter & Gamble Company, 1983). The laboratory rodents were exposed to 0, 10, 32, or 100 mg/kg/day maleic anhydride in feed, seven days a week for two years. There is no indication that maleic anhydride has a carcinogenic potential

The registrant submitted a guideline comparable study (OECD TG 416: Two generation reproduction toxicity study) for the evaluation of the effects of maleic anhydride on the fertility and development (Monsanto Company, 1982, Short et al., 1981).

Original study has been available to the evaluating member state. The presented studies are applicable for hazard characterization, although some deviations from the test guideline have been encountered. There is no evidence that maleic anhydride has any adverse effects to the reproduction system or adverse outcomes on the development.

Test result demonstrates that maleic anhydride is an acute toxic substance (oral route) and possesses corrosive and sensitizing potential. Evaluation of individual endpoint revealed that the Annex VI entry is incomplete and data are present which demonstrate that maleic anhydride warrants further harmonized classification for Eye damage 1 (H318: Causes serious eye damage), STOT RE 1(H372: Causes damage to the respiratory tract through prolonged or repeated exposure), STOT RE 2 (H373: May cause damage to the kidneys through prolonged or repeated exposure), a sub-classification of Skin Sens 1A (H317: May cause an allergic skin reaction) and furthermore a label with EU H071 (Corrosive to the respiratory tract) is deemed necessary.

Assessment of concerns subject to evaluation: human exposure

The human exposure assessment was amended by the registrants based on the comments and feedback of the evaluating member state. This is a summary of the current versions given in the current registration dossiers.

Maleic anhydride is considered to be a skin and respiratory sensitizer with high potency. For worker exposure, respiratory sensitization was identified as key toxicological concern for risk assessment. Based on the available data without reliable quantitative information, the registrants decided not to derive long or short term DNELs for this most sensitive endpoint.

The pure substance maleic anhydride as manufactured is corrosive.

Referring to these properties, contact of man with this substance needs to be prevented and potential exposure as low as feasible.

Given that it is not possible to derive thresholds for these effects, a qualitative assessment was carried out by the registrants.

Maleic anhydride is intended for following uses under the scope of REACH. The substance is used only by workers at industrial sites.

1) Manufacture of substance (flakes; low dustiness)
2) Manufacture of substance (melting; 77°C)
3) Industrial use as an intermediate in chemical synthesis (flakes; low dustiness)
4) Industrial use as an intermediate in chemical synthesis (melting; 77°C)
5) Use as monomer in polymerization reactions (flakes; low dustiness)
6) Use as monomer in polymerization reactions (melting, 77°C)

All of these uses cover the processes: PROC 1, PROC 2, PROC 3, PROC 8b and PROC 15.

PROC 1 - Use in closed process, no likelihood of exposure

PROC 2 - Use in closed, continuous process with occasional controlled exposure

PROC 3 - Use in closed batch process (synthesis or formulation)

PROC 8b - Transfer of chemicals from/to vessels/ large containers at dedicated facilities

PROC 15 - Use of laboratory reagents in small scale laboratories

Maleic anhydride is manufactured/applied in two forms: the molten state and flakes (low dustiness). Molten maleic anhydride is produced at a temperature of approximately 77°C and is also hazardous by virtue of its temperature and specific heat (i.e. danger from scalding).

Maleic anhydride is produced/used under controlled conditions in high integrity contained systems (PROC 1, 2, 3), with little or no potential for exposure of operators. Installations involved in the production/use of maleic anhydride are variously in the open air (outdoor), under cover (i.e. outdoor but with a roof and open sides), and in enclosed buildings. Enclosed buildings have got LEV.

Many processes of the given uses are computer controlled, with the supervising operators working in dedicated plant control rooms. If exposure can be excluded like possibly in the plant control rooms, workers are not required to wear full PPE. However, they will need to follow the standard practices of the production unit for safety reasons.

Measured data of maleic anyhdride indicate that emissions during various activities are possible, despite of the technical measures at the sites. Workers are therefore required to wear full PPE (chemical resistant clothing and boots) and RPE (respirator with an organic filter) in order to avoid being sensitized by inhalation and by dermal contact, if contact is possible e.g. sampling, maintenance, etc.

Employees of the manufacturing sites are fully trained and licensed to work with maleic anhydride. Prior to start working at facilities dealing with maleic anhydride, a complete history and physical examination is carried out to detect any pre-existing conditions.

Based on the chemical forms of maleic anhydride, the most likely routes of worker exposure are via dermal contact and inhalation. Oral exposure is not considered to be relevant and would only occur under intentional exposure which is outside the scope of REACH. It is also considered to be unlikely that humans will be exposed indirectly either by way of contact with the air, surface waters or soils, or by way of drinking water, or through exposure in the food chain, because maleic anhydride is readily biodegradable in atmospheric, aquatic and soil compartments, and does not bio-accumulate.

The registrants ensure that workers involved in the production and use of maleic anhydride are protected by the nature of the installations, use of PPE and RPE, if potential for contact exists and use of controlled procedures. In addition, medical monitoring of the workers is also used as a mean of risk management.

Based on the received data and descriptions, 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 as low as feasible. The currently applied measures are considered to be applicable for ensuring safe use and preventing sensitization of workers. Therefore, the covered industrial uses are considered to reveal an acceptable risk. No further data were considered to be required.

Conclusions	**Tick box**
Need for follow up regulatory action at EU level	
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

Maleic anhydride has an Annex VI entry according to the CLP Regulation and is harmonized classified as Acute Tox 4 (H302: harmful if swallowed), Skin corrosive 1B (H314: causes severe skin burns and eye damage), Skin Sens. 1 (H317: may cause an allergic skin reaction), Resp. Sens. 1 (H334: May cause allergy or asthma symptoms or breathing difficulties if inhaled).

Test result demonstrates that maleic anhydride is an acute toxic substance (oral route) and possesses corrosive and sensitizing potential. Evaluation of individual endpoint revealed that the Annex VI entry is incomplete and data are present which demonstrate that maleic anhydride warrants further harmonized classification for Eye damage 1 (H318: Causes serious eye damage), STOT RE 1(H372: Causes damage to the respiratory tract through prolonged or repeated exposure), STOT RE 2 (H373: May cause damage to the kidneys through prolonged or repeated exposure), a sub-classification of Skin Sens 1A (H317: May cause an allergic skin reaction) and furthermore a label with EU H071 (Corrosive to the respiratory tract) is deemed necessary.

A harmonized classification and labelling according to Regulation (EC) No 1272/2008 for these endpoints is deemed necessary in order to ensure safe handling and appropriate use of maleic anhydride, as the Annex VI entry of this substance is incomplete and data are present which demonstrate that maleic anhydride warrants further harmonized classification.

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

Not applicable.

3.1.3. Need for restrictions

Not applicable.

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

Not applicable.

3.2. NO FOLLOW-UP ACTION NEEDED

Not applicable.

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

Indication of a tentative plan is not a formal commitment for the evaluating Member State. A formal commitment to prepare a REACH Annex XV dossier (SVHC, restrictions) and/or CLP Annex VI dossier shall be made via the Registry of Intentions.

Follow-up action	Date for intention	Actor
CLP Annex VI dossier	open	Austria

References:

Confidential (1983). In vivo Bone Marrow Chromosome Study in Rats (Inhalation exposure). Testing laboratory: Hazleton Laboratories America, Inc. Report no.: 241-142. Owner company: Monsanto. Report date: 1983-02-06. (also cited in OECD SIDS, 2004)

Goldenthal, E. I.; Jessup, D. C., and Geil, R. G. (1979). Four-week inhalation study in rats. Testing laboratory: International Research and Development Corporation. Owner company: Monsanto. Report date: 1979-02-15.

Humiston, C. G.; Frauson, L. A.; Quast, J. F., and Wade, C. E. (1975). Maleic Anhydride: results of a 90-day dietary feeding study in rats. Testing laboratory: Toxicology research laboratory, Dow Chem Co. Report no.: D-1248. Owner company: Dow Chemical Company. Report date: 1975-04-01 (also cited in OECD SIDS, 2004)

Monsanto Company (1982). Three Generation Reproduction Study in Rats (Modified to a Two Generation Study). Testing laboratory: International Research and Development Corporation. Report no.: 401-089a. Owner company: Monsanto Company. Report date: 1982-09-22.

MAK (Maximale Arbeitsplatzkonzentration), 1991. Maleinsäureanhydride. The MAK Collection for Occupational Health and Safety. Published Online : 31 JAN 2012, DOI: 10.1002/3527600418.mb10831d0017. pp. 14

MAK (Maximale Arbeitsplatzkonzentration), 1995. Nachtrag. Maleinsäureanhydride. The MAK Collection for Occupational Health and Safety Published Online : 31 JAN 2012, DOI: 10.1002/3527600418.mb10831d002. pp. 2

MAK (Maximale Arbeitsplatzkonzentration), 2000. Maleinsäureanhydride. The MAK Collection for Occupational Health and Safety. Published Online : 31 JAN 2012, DOI: 10.1002/3527600418.mb10831d0030

OECD SIDS (Screening Information Dataset) (2004). Maleic Anhydride and Maleic Acid, SIDS Initial Assessment Report for SIAM 18 Paris, France, 20-23 April 2004

Procter & Gamble Company (1983). Chronic Dietary Administration of Maleic Anhydride. Testing laboratory: CIIT, Research Triangle Park. Report no.: IITRI-L8026-6B. Owner company: Procter & Gamble Company. Report date: 1984-10-23. (also cited in OECD SIDS, 2004)

Short, R. D., Johannsen, F. R., Ulrich, C. (1981). Six-month multispecies inhalation toxicity study; published in Fund. and Appl. Toxicol. 10: 517-524, 1988.

U.S. EPA (1986). Health and Environmental Effects Profile for Maleic Anhydride. NTIS, U. S. EPA, Report. EPA/600/X-86/196.