SUBSTANCE EVALUATION REPORT

Public Name: Maleic anhydride

EC Number(s): 203-571-6

CAS Number(s): 108-31-6

Submitting Member State Competent Authority:

Environment Agency Austria, 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)

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Conclusions of the most recent evaluation step*	Tick relevant box(es)
Concern not clarified; Need to request further information from the Registrant(s) with the draft decision	
Concern clarified; No need of further risk management measures	
Concern clarified; Need for risk management measures	x
Other:	

**Include details in the executive summary.*

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Executive summary

Grounds for concern

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 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 tasks 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 registrant 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 was 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 has 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 sensitising 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 reproductive toxicity were assessed by the evaluating member state for verifying, if the studies used by registrants are sufficient and valid to determine the hazard. One rat carcinogenicity study is available, which has several deficiencies. Furthermore, the reproductive toxicity 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 sensitisation 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.

Procedure

The evaluation of the toxicity of maleic anhydride was based on data provided by the registrants (IUCLID dossiers, CSRs and original studies). In addition, comprehensive reviews performed by international bodies/regulatory programs and original publications were taken into consideration. Maleic anhydride was reviewed for example by the OECD HPV Chemicals Programme in the year 2004 (SIDS Dossier, OECD SIDS, 2004), by the U.S. Environmental Protection Agency (US EPA, 1986), the German Senate Commission for the Testing of Harmful Working Materials (MAK Commission,1991, 1995, 2000). If it was considered relevant, the original publications and/or study reports were assessed as indicated in the text. Furthermore, following on-line databases were screened to gather further relevant information: Hazardous Substances Data Bank (HSDB)- United States National Library of Medicine, Integrated Risk Information System (IRIS) – Environmental Protection Agency, Chemical Carcinogenesis Research Information System (CCRIS), Toxline, CHEMIDPLUS and ToxNet. The evaluation was targeted to all sections of the chemical safety assessment.

After a detailed review of the registration data and the provided studies by experts of the evaluating member state, comments and recommendations for amendments were sent to the registrants. The identified concerns and proposals were discussed between the experts of the evaluating member state and registrants. The update of the registration data (IUCLID file, CSR) was uploaded in October 2013. As the available data and the data provided by the registrants during substance evaluation were considered to be sufficient for drawing conclusions, no new data/tests were considered to be required. The updated dossier is considered to be a key output of this evaluation.

The assessment of the amended registration dossiers and new data source is summarized in the following.

Summary of human health hazard assessment

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 (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.

Summary of human exposure assessment

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.

Summary of environmental fate properties and environmental hazard assessment

The assessment of the environmental part of the maleic anhydride dossier did not reveal a concern which would lead to the necessity to ask for more data.

Maleic anhydride hydrolyses rapidly forming the hydrolysis product maleic acid. Maleic anhydride and maleic acid are readily biodegradable, no persistence needs to be expected.

Maleic anhydride comprises a low log Pow value (-2.61). Also, there is no indication from human health section for bioaccumulation. Therefore, no bioaccumulation needs to be expected.

Estimations for the Henry´s law constants for maleic anhydride and its hydrolysis product maleic acid show very low values suggesting that maleic anhydride or maleic acid will not likely evaporate from water surfaces to the air.

Toxicity can be considered to be moderate: The most sensitive species in acute tests was reported to be daphnids: In the key study on the acute toxicity of the hydrolysis product maleic acid to Daphnia magna an 48h-EC_{50} of 42.81 mg/L was reported with a non-neutralized test solution (DSM 2010). The pH adjusted test solution showed a decrease in effects (48h-EC_{50} = 93.8 mg/L). Nevertheless in a conservative approach the test performed with the non-neutralised test solution was used as key value. The key studies for freshwater fish and algae revealed a 96 h-LC_{50} of 75 mg/L and a 72 h-EC_{50} for freshwater algae of 74.35 mg/L (based on growth rate).

The results of a chronic daphnia study are also reported (21d-NOEC: 10 mg/L), but the provided study description is too scarce (Klimisch score: 4) to make this study usable for chemicals risk assessment. Therefore the PNEC water needs a revision using the lowest assignable and reliable value from aquatic acute toxicity studies.

In the key study for sewage treatment plants microorganisms using *Pseudomonas putida* a 18h-EC_{10} of 44.6 mg/L based on growth inhibition for maleic anhydride was gained.

Regarding the classification of maleic anhydride for the environment the evaluating member state agrees that the data available do not provide a basis warranting classification.

Summary of environmental exposure assessment

A quantitative assessment was not performed by the registrants. Nevertheless, the registrants provided more detailed information on the uses and the risk management measures at sites. Regarding the indicated industrial uses, significant releases of maleic anhydride to the environment are not expected. The substance is consumed during their final uses and is kept in closed systems during the processes. Losses during manufacture and use are avoided as far as feasible and estimated to be not relevant referring to the waste management at sites (e.g. treatment of emissions to water and air). Regarding the indicated uses and the properties of the substance, the sewage treatment plant is expected to be the main receiving compartment. Rapid hydrolysis of maleic anhydride to maleic acid and ready biodegradability of these substances suggest that small amounts of release will rapidly disappear from water and soil via mineralisation. Furthermore, the low log Pow suggest that the substance is not bio-accumulative. The indicated uses and the substance give no reason for concern and for requesting further data.

Conclusions

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

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 Corr. 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 results demonstrate 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). 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 the aforementioned endpoints is deemed necessary in order to ensure safe handling and appropriate use of maleic anhydride.

A comparison between already harmonized classification entry in Annex VI of the Regulation (EC) No 1272/2008 and the further needed harmonized classification is depicted in the following table.

Table: Overview of harmonised classification entry[1] and proposed amendment of the entry

	Classification		**Labelling**
	Hazard Class and Category Code(s)	**Hazard Statement Code(s)**	**Hazard Statement Code(s)**
Harmonised classification[1]	Acute Tox 4 Skin Corr. 1B Skin Sens. 1 Resp. Sens. 1	H302 H414 H317 H334	H302 H414 H317 H334
Further warranted classifications /subclassifications/labelling	Eye damage 1 Skin Sens 1A STOT RE 1[2] STOT RE 2[3]	H318 H317 H372[2] H373[3]	H318 H317 H372[2] H373[3] EU H071

[1]Regulation (EC) No 1272/2008, Annex VI (Table 3.1.)

[2]H372: Causes damage to the respiratory tract through prolonged or repeated exposure (inhalation)

[3]H373: May cause damage to kidney through prolonged or repeated exposure (oral)

References:

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