Committee for Risk Assessment

RAC

Opinion

proposing harmonised classification and labelling
at EU level of

maleic anhydride

EC Number: 203-571-6
CAS Number: 108-31-6

CLH-O-0000001412-86-121/F

Adopted

16 September 2016

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CLH-O-0000001412-86-121/F

OPINION OF THE COMMITTEE FOR RISK ASSESSMENT ON A DOSSIER PROPOSING HARMONISED CLASSIFICATION AND LABELLING AT EU LEVEL

In accordance with Article 37 (4) of Regulation (EC) No 1272/2008, the Classification, Labelling and Packaging (CLP) Regulation, the Committee for Risk Assessment (RAC) has adopted an opinion on the proposal for harmonised classification and labelling (CLH) of:

Chemical name: **maleic anhydride**

EC Number: **203-571-6**

CAS Number: **108-31-6**

The proposal was submitted by **Austria** and received by RAC on **18 November 2015.**

In this opinion, all classification and labelling elements are given in accordance with the CLP Regulation.

PROCESS FOR ADOPTION OF THE OPINION

Austria has submitted a CLH dossier containing a proposal together with the justification and background information documented in a CLH report. The CLH report was made publicly available in accordance with the requirements of the CLP Regulation at ***http://echa.europa.eu/harmonised-classification-and-labelling-consultation/*** on **9 December 2015**. Concerned parties and Member State Competent Authorities (MSCA) were invited to submit comments and contributions by **25 January 2016**.

ADOPTION OF THE OPINION OF RAC

Rapporteur, appointed by RAC: **Bert-Ove Lund**

Co-Rapporteur, appointed by RAC: **Anne-Lee Gustafson**

The opinion takes into account the comments provided by MSCAs and concerned parties in accordance with Article 37(4) of the CLP Regulation and the comments received are compiled in Annex 2.

The RAC opinion on the proposed harmonised classification and labelling was adopted on **16 September 2016** by **consensus.**

Classification and labelling in accordance with the CLP Regulation (Regulation (EC) 1272/2008)

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard state-ment Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	607-096-00-9	maleic anhydride	203-571-6	108-31-6	Acute Tox 4* Skin Corr. 1B Skin Sens. 1 Resp. Sens. 1	H302 H314 H317 H334	GHS07 GHS08 GHS05 Dgr	H302 H314 H317 H334			
Dossier submitters proposal	607-096-00-9	maleic anhydride	203-571-6	108-31-6	**Retain** Skin Corr. 1B Resp. Sens. 1 **Add** Eye dam. 1 STOT RE 1 STOT RE 2 **Modify** Acute Tox 4 Skin Sens. 1A	**Retain** H314 H334 H302 H317 **Add** H318 H372 (respiratory system) H373 (kidney)	**Retain** GHS07 GHS08 GHS05 Dgr	**Retain** H314 H334 H302 H317 **Add** H372 H373	**Add** EUH071		
RAC opinion	607-096-00-9	maleic anhydride	203-571-6	108-31-6	**Retain** Skin Corr. 1B Resp. Sens. 1 **Add** Eye dam. 1 STOT RE 1 **Modify** Acute Tox 4 Skin Sens. 1A	**Retain** H314 H334 H302 H317 **Add** H318 H372 (respiratory system)	**Retain** GHS08 GHS05 Dgr **Remove** GHS07	**Retain** H302 H314 H317 H334 **Add** H372 H373	**Add** EUH071		
Resulting Annex VI entry if agreed by COM	607-096-00-9	maleic anhydride	203-571-6	108-31-6	Acute Tox 4 STOT RE 1 Skin Corr. 1B Eye Dam. 1 Resp. Sens. 1 Skin Sens. 1A	H302 H372 (respiratory system) H314 H318 H334 H317	GHS08 GHS05 Dgr	H302 H372 (respiratory system) H314 H334 H317	EUH071		

GROUNDS FOR ADOPTION OF THE OPINION

RAC general comment

Maleic anhydride was discussed by the Technical Committee on Classification and Labelling (TC C&L) and classified under Commission Directive 98/73/EC in 1998 as Acute Tox. 4* (oral), Skin Corr. 1B, Skin Sens. 1, and Resp. Sens. 1).

The present proposal by the Dossier Submitter (DS) was based on a Substance Evaluation (ECHA, 2014) recently performed under REACH and accordingly, only the endpoints recommended in this report are assessed (acute oral toxicity, eye irritation/damage, respiratory tract irritation, skin sensitisation, and repeated dose toxicity).

It should be noted that maleic anhydride is a reactive substance that quickly hydrolyses to maleic acid in aqueous solutions. The anhydride is, however, soluble and stable in non-aqueous media, which have therefore been used for most studies. Studies using non-aqueous solutions of maleic anhydride are preferred and are given a greater weight in the analysis.

HUMAN HEALTH HAZARD EVALUTATION

RAC evaluation of acute toxicity

Summary of the Dossier Submitter's proposal

The dossier refers to two reliable oral studies in rats, with the substance dissolved in distilled water in one study (Murmann, 1984) and in Lutrol® in the other (Löser, 1978). A combined LD_{50} for males and females of 1090 mg/kg was determined by Murmann (1984). Löser (1978) only studied males and obtained a LD_{50} of 1030 mg/kg. Irrespective of solvent, the anhydride is expected to quickly hydrolyse to maleic acid in the gastrointestinal tract, and both studies are therefore considered relevant by the DS. Both LD_{50} values are in the range of 300-2000 mg/kg and are supportive of classification as Acute Tox. 4 (H302), thereby confirming (and leading to removal of the asterix) of the present minimum classification. The dossier submitter additionally noted that there are many other acute oral studies, which are not considered reliable, but still give LD_{50} values in the range relevant for Acute Tox. 4.

Comments received during public consultation

One MS supported the proposal, and none opposed it.

Assessment and comparison with the classification criteria

RAC notes that both studies predate the OECD Guidelines and have some shortcomings. Although Löser (1978) only used male rats, RAC considers that this study is more reliable than Murmann (1984) since Löser (1978) used a vehicle that prevented hydrolysis of the anhydride already in the vehicle, before administration of the substance. Nevertheless, it seems plausible that hydrolysis of the anhydride to maleic acid will be very rapid in the gastrointestinal tract.

Therefore, RAC agrees with the DS that the results of both studies (1030 and 1090 mg/kg) support retaining **Acute Tox. 4; H302 and removal of the asterisk** for the minimum classification.

RAC evaluation of specific target organ toxicity – single exposure (STOT SE)

Summary of the Dossier Submitter's proposal

The hazard class STOT SE is not evaluated in the CLH proposal from the DS. However, the CLH report described human data (e.g. case reports and questionnaires) which indicated adverse effects on the respiratory tract, such as serious coughing, reddened mucous membranes of the nose and throat, work-related wheeze and breathlessness. Since the mode of action is corrosivity, the Dossier Submitter (DS) considers that maleic anhydride also needs to be labeled as EUH071 (Corrosive to the respiratory tract).

Comments received during public consultation

One MS supported the proposal (labelling with EUH071), and none opposed it.

Assessment and comparison with the classification criteria

The human data presented indicate respiratory tract irritation, but these data are not very robust, and probably not sufficient for classification as STOT SE 3. Acute inhalation toxicity was not assessed in the CLH proposal but one old and rather poor acute inhalation study was described. In this study, 4 rats, 1 cat, 1 rabbit, 1 guinea pig, and 10 mice were exposed for 1 hour to 4.35 mg/L maleic anhydride (BASF, 1953). The guinea pig and 4 mice died, possibly indicating LC_{50} values in the mg/L order of magnitude. The respiratory system may be the target organ, but the study is not sufficiently robust to allow classification with STOT SE 3.

The corrosivity of maleic anhydride is, however, clear, and as the substance is not classified for acute inhalation toxicity or STOT SE 3, the proposal for **additional labelling with EUH071 (corrosive to the respiratory tract)** is supported by the CLP Regulation (Annex II, 1.2.6) and by RAC.

RAC evaluation of skin corrosion/irritation

Summary of the Dossier Submitter's proposal

The substance is already classified as Skin Corr. 1B, and the endpoint has not been further analysed. Therefore, this endpoint was not open for commenting in the public consultation.

Comments received during public consultation

No comments were submitted for this hazard class.

Assessment and comparison with the classification criteria

RAC notes that no data was presented in the CLH report, but that maleic anhydride is already classified for Skin Corrosion (1B).

RAC evaluation of serious eye damage/irritation

Summary of the Dossier Submitter's proposal

The key study is reliable, performed according to GLP and comparable to OECD TG 405 (IIT Research Institute, 1981). Undiluted maleic anhydride in the form of crystals was applied to rabbit eyes. The rabbits were killed after 48 hours because of signs of severe eye damage, pain and discomfort. At this time point, the corneal opacity score was $\geq$ 3 and the iritis score $\geq$ 1.5, fulfilling the criteria for Eye Damage 1 (H318). Eye damage and irreversible effects were also observed in the supporting studies, in which an oily or undefined solution of maleic anhydride was applied to the eyes. Maleic anhydride is currently classified with H314 (Causes severe skin burns and eye damage). The DS proposed additional classification with Eye Damage 1, H318 (see Table 2 of the background document). However, in the text the DS proposed no labelling/hazard phrase for eye damage (i.e no use of H318: causes serious eye damage) as it would lead to duplication of information as the eye is already mentioned in H314.

Comments received during public consultation

One MS supported the proposal, and none opposed it.

Assessment and comparison with the classification criteria

Almost maximum scoring for corneal opacity, iris lesion, and conjunctival erythema/chemosis were observed in rabbits administered maleic anhydride crystals (needles) and the rabbits were accordingly killed at 48 hours because of excess toxicity (IIT Research Institute, 1981). An additional physical effect of the crystals is possible, but the effects seem too severe to be explained exclusively by a physical effect of the crystal needles. Furthermore, as also an oily solution of maleic anhydride caused irreversible eye damage in the BASF (1953) study, it seems that it is the reactive substance itself causing the eye damage. The reporting of the BASF (1953) study is poor, but a 10% solution in oil resulted in redness, swelling, corneal opacity, blood discharge, and after 6 weeks scarring. In a third study (Winter, 1950), 1 or 5% solutions of maleic anhydride (vehicle not defined) were applied to rabbit eyes, which were then rinsed after 2 minutes. Cloudiness of the cornea and irritation were observed initially, but they were reversible. When fine powder was applied to two rabbits, there was immediate clouding of the cornea, and later oedema, inflammation and corneal ulcers.

There are shortcomings with all the available studies, but in light of the clear effects reported in them, the known reactivity of anhydrides, and that the substance already has a harmonised classification for corrosivity (data not provided in the CLH report), RAC supports classification with Eye Dam. 1; H318.

Concerning classification for both skin corrosion and eye damage, the Commission has explained that skin corrosive substances should additionally be classified as **Eye Dam. 1; H318**. However, separate labelling with 'H318: Causes serious eye damage' is not needed since the eye damage hazard is already mentioned by the hazard statement under labelling for skin corrosive substances (H314, Causes severe skin burns and eye damage).

RAC evaluation of skin sensitisation

Summary of the Dossier Submitter's proposal

Two reliable guideline comparable studies demonstrated a high skin sensitising potential of maleic anhydride. The current classification is Skin Sens. 1, but based on an EC3 < 2% in an LLNA study and a Buehler test with > 60% of animals responding to a topical induction concentration of 5%, sub-category 1A is proposed (Skin Sens 1A; H317).

Comments received during public consultation

Three MS supported the proposal, and none opposed it. Two of the MS also proposed setting a SCL of 0.001% based on extreme potency.

Assessment and comparison with the classification criteria

As maleic anhydride is already classified for skin sensitisation in Category 1, the evaluation focuses on whether the data allows a sub-categorisation (1A or 1B). An LLNA study using 0-2.5% concentrations of maleic anhydride in acetone/olive oil, gave a dose-dependent increase of the stimulation index, with a three-fold increase (EC3) with 0.16% maleic anhydride. There were some deviations from the guideline, but considering the clearly positive results they are not considered to decrease the reliability of the data. A Buehler test (OECD TG 406) using 5% maleic anhydride in mineral oil for induction and 0.5% in mineral oil for challenge gave positive reactions in all 20 animals (scores 0.5-2.0) whereas no reactions were observed in the controls (score 0.0). There were two additional old animal studies (in guinea pigs) and human data mentioned in the CLH report suggestive of sensitisation, but they are not suitable for sub-categorisation. The criteria for Cat. 1A are an EC3 value ≤ 2% in the LLNA and ≥ 60% of the animals responding at induction concentrations of 0.2-20% in the Buhler test. Both these criteria are fulfilled (EC3 = 0.16%; 100% responding in the Buehler test) and **Skin Sens. 1A; H317** is therefore supported by RAC.

The CLH report did not address the need for an SCL. However, in the RCOM, the DS supports a SCL of 0.001% based on an extreme potency, as suggested in two comments received during public consultation. RAC agrees with the conclusion that the LLNA indicates an extreme potency (EC3 < 0.2%) and that the Buehler test indicates at least a strong potency. Considering that the LLNA is the preferred test, the data support an **SCL of 0.001%**.

RAC evaluation of respiratory sensitisation

Summary of the Dossier Submitter's proposal

Maleic anhydride is currently classified for respiratory sensitisation (H334), but the CLH dossier did not evaluate this endpoint.

Comments received during public consultation

Three MSs noted the present classification with Resp. Sens 1 (H334) and the lack of data for assessing this classification and a potential sub-categorisation. It was proposed by one MS to consider the animal study on respiratory sensitisation reported in the REACH registration.

Assessment and comparison with the classification criteria

RAC notes the present classification for respiratory sensitisation (Category 1), and concludes that there are no data available to support further sub-categorisation for respiratory sensitisation.

RAC evaluation of specific target organ toxicity– repeated exposure (STOT RE)

Summary of the Dossier Submitter's proposal

Oral toxicity

According to the DS, toxic effects to the kidneys were seen to occur within the guidance value (GV) range of 10 < C < 100 mg/kg/day for classification in STOT RE 2 in male rats exposed to maleic anhydride for 90 days. The results were reproducible but it is acknowledged that the effects at 100 mg/kg/day were minor (a slight not statistically significant increased kidney weight, pale discoloration, and, in 5 out of 15 male rats, mild renal tubular dilation hypertrophy and mild degeneration of the tubular cells in the cortical portion of the nephron). At higher dose levels ($\geq$ 250 mg/kg/day), the effects were more severe. However, since the GVs are only for guidance purposes, a STOT RE 2 classification is proposed for kidney effects after oral exposure (oral, kidney; H373).

Inhalation toxicity

In the study of Goldenthal *et al.* (1976), Sprague-Dawley rats were exposed to 0, 0.012, 0.032, or 0.086 mg/L maleic anhydride, which caused dose-dependent toxicity in the respiratory system. The findings included (1) haemorrhagic foci in the lung (dose-dependent, higher in medium and high exposure groups), (2) dark red lung foci, congestion, haemorrhage and localised atelectasis (medium and high dose groups), (3) squamous metaplasia, inflammatory infiltrate in the mucosa of the trachea and nasal turbinates, epithelial hyperplasia in turbinates (all exposure groups), (4) intravascular haemorrhage and presence of foamy macrophages in alveoli (all exposure groups), (5) keratitis and corneal vascularisation (highest dose group).

The multispecies 6 months study of Short et al. (1981) supports the findings of Goldenthal et al. (1976). The GV for a 28 days inhalation study is ≤ 0.6 mg/L (vapour) for adverse effects that warrant classification with STOT RE 1. According to the DS, as adverse respiratory effects were observed at concentrations much below this GV, maleic anhydride should be classified as STOT RE 1 (H372: causes damage to respiratory system through prolonged or repeated exposure by inhalation).

With regard to the known corrosivity of maleic anhydride, and the possible relation to acute effects induced by corrosion, the CLP Guidance states that if the toxic concentration in a repeated dose study is more than half an order of magnitude lower than that mediating the evident acute toxicity (corrosivity) then it should be considered a repeated dose toxicity effect. For maleic anhydride the repeated dose toxicity occurred at a dose level of 0.01 mg/L maleic anhydride (duration of exposure 28 days). The only available acute study (BASF, 1953) indicates an LC50 in the order of a few mg/L, which is far above the repeated dose LOAEL (0.01 mg/L). Therefore, according to the DS, classification for repeated dose toxicity is relevant.

Comments received during public consultation

Two MSs argued that the kidney toxicity observed after oral exposure does not meet the criteria for STOT RE 2 as the kidney effects at dose levels below the GV are not really adverse. One MS

and one industry organisation also pointed out that STOT RE 1 and STOT RE 2 cannot be used in parallel for the same substance. Regarding toxicity after inhalation, two MS supported the proposal for STOT RE 1, and none opposed it.

Assessment and comparison with the classification criteria

Repeated dose toxicity - oral

The kidney is a target organ for maleic anhydride, but only the 90 days rat study by Humiston *et al.* (1975) has indicated effects at doses in the range of the GVs for STOT RE 2 (10-100 mg/kg/day). The effects at 100 mg/kg/day were described as mild, and included renal tubular dilation, hypertrophy, and degeneration of the tubular cells in the cortical portion of the nephron in 5 out of 15 male rats. No kidney effects were observed in females. These mild effects are borderline to qualifying as adverse in the context of the classification criteria for STOT RE. At 250 mg/kg/day, a dose level 2.5-fold greater than the GV, the effects were clearly adverse with 10 out of 15 male rats affected (5 animals: minimal changes, 4 animals: moderate changes, 1 animal severe changes) (Humiston *et al.*, 1975). Adverse effects at 250 mg/kg/day were also observed in the other 90 day rat study (Humiston *et al.*, 1977), but lower doses were not investigated. The borderline adverse effects at 100 mg/kg/day have to be considered in conjunction with not finding any kidney effects in the 2 year rat study up to dose levels of 100 mg/kg/day. It is, however, noted that the 90 days studies were performed using Sprague-Dawley rats, whereas the 2 year study used Fischer rats, possibly indicating differences in sensitivity between different rat strains.

The DS also refers to the 2-generation study by Short (1982) as a supportive study. However, RAC is of the opinion that adverse kidney effects were only observed in F0 animals of the top dose (150 mg/kg/day). Furthermore, 20 out of 30 F0 and all female F1 animals died at this dose (pneumonia, septicaemia and/or kidney toxicity were stated as causes of death), making it difficult to draw any conclusions from this study.

In a weight of evidence analysis the following factors have been considered;

- borderline adverse effects only in male rats at 100 mg/kg/day (Humiston *et al.*, 1975),
- the lack of effects at 100 mg/kg/day in the 2 year rat study,
- longer studies carry a greater weight with regard to STOT RE,
- no adverse kidney effects were observed within the corrected GVs in the 2-generation rat study (corrected for a duration of 210 days),
- and no kidney effects were observed in a 90 days study in dogs ($\leq$ 60 mg/kg/day).

The table below presents a summary of the kidney effects observed in repeated toxicity studies.

Study (species, duration, doses)	**GVs for STOT RE 2**	**LOAEL - effects**	**Reference**
Rat – 90 days; 0, 20, 40, 100, 250, 600 mg/kg/day	10 < GV $\leqslant$ 100 mg/kg bw/day	100 – mild kidney effects	Humiston *et al.*, 1975
Rat – 90 days & 183 days; 0, 250, 600 mg/kg/day	10 < GV $\leqslant$ 100 5 < GV $\leqslant$ 50 mg/kg bw/day	250 – kidney weight +24% 250 – kidney weight +54% At both time-points dose-related ↑ in degenerative, hypertrophic, and regenerative changes	Humiston *et al.*, 1977

Rat – 2-generation F0 - 210 days; 0, 20, 55, 150 mg/kg/day	4.3 < GV ⩽ 43 mg/kg bw/day	150 – renal cortical necrosis Other renal changes were randomly distributed among groups	Short, 1982
Rat – 2 year 0, 10, 32, 100 mg/kg/day	1.25 < GV ⩽ 12.5 mg/kg bw/day	No effects on kidney	Procter & Gamble Company (1983)
Dog - 90 days 0, 20, 40, 60 mg/kg/day	10 < GV ⩽ 100 mg/kg bw/day	No adverse effects	Braun *et al.*, 1975

Although the kidney is clearly a target organ after repeated exposure, RAC is of the opinion that the potency is not sufficient to warrant classification with STOT RE 2 for the oral route. Besides, RAC concludes that classifying maleic anhydride with STOT RE 1 for toxic effects in the respiratory system (see next section) STOT RE 2 is no longer relevant.

Repeated dose toxicity - inhalation

A reliable 28 day whole-body inhalation study in rats (with exposure 6 hours/day for 5 days a week) was performed according to OECD TG 412. The concentration of maleic anhydride in the cages was confirmed by gas chromatography to be 0, 0.012, 0.032 and 0.086 mg/L. Dose-dependent toxicity was observed in the respiratory system. All concentrations are below the GV for a 28 day study for STOT RE 1 (≤ 0.6 mg/L vapour), and the following description of symptoms therefore focuses on the high dose group. Clinical signs included episodes of nasal bleeding and marked respiratory distress. Keratitis and/or corneal vascularisation were observed in several rats, as well as haemorrhagic foci in the lungs, adhesions, congestion and localised atelectasis. Histopathology confirmed squamous metaplasia in the upper respiratory tract, inflammatory infiltrate and hyperplasia in the mucosa of the trachea and nasal turbinates. Compound-related lung lesions included bronchial epithelia hyperplasia and squamous metaplasia. Localised intra-alveolar haemorrhage and presence of foamy macrophages in alveoli were noted in all three exposure groups. It is noted that the information from the study is qualitative rather than quantitative, making a thorough independent assessment of the results difficult. However, the overall pattern of effects, the dose-dependency, the known corrosivity of maleic anhydride, and effects occurring at low exposure levels, argues for sufficiently adverse effects to qualify for a STOT RE 1 classification.

Respiratory toxicity was also observed in the study by Short *et al.* (1988) where rats, hamsters and rhesus monkey were exposed for 6 months (6 hours/day for 5 days a week) to concentrations of 0, 0.0011, 0.0033, and 0.0098 mg/L. Concentrations were confirmed by GC, but the animals were apparently exposed to a mixture of maleic anhydride and maleic acid. The study is therefore not assessed quantitatively by RAC.

As pointed out by the DS, it has to be evaluated whether the effects should be considered acute or as a consequence of repeated dose toxicity. Acute inhalation toxicity is not assessed in the CLH proposal but one old and rather poorly executed acute inhalation study is described in the CLH proposal. In this study, 4 rats, 1 cat, 1 rabbit, 1 guinea pig, and 10 mice were exposed for 1 hour to 4.35 mg/L maleic anhydride (BASF, 1953). The guinea pig and 4 mice died, possibly indicating LC_{50}-values in the mg/L order of magnitude. Considering that adverse effects occurred in the 28 days study at exposure levels < 0.09 mg/L, thus more than half an order of magnitude lower than the concentration suggested by the BASF study (1953) to mediate acute inhalation toxicity, and the fact that maleic anhydride is not classified for acute inhalation toxicity, classification for repeated dose toxicity is relevant.

RAC therefore agrees with the proposal of the DS to classify maleic anhydride as **STOT RE 1 (H372: causes damage to respiratory system through prolonged or repeated exposure)**.

Additional references

A clarification regarding the 2-generation study by Short (1982); *Short (1982). Three Generation Reproduction Study in Rats (modified to a two generation study). Maleic Anhydride. International research and development corporation project No: IR-19-358.* The study is partly published in: *Short RD, Johannsen FR, Levinskas GJ, Rodwell DE, Schardein JL (1986).Teratology and multigeneration reproduction studies with maleic anhydride in rats. Fundam Appl Toxicol. Oct;7(3):359-66.*

ECHA. 2014. Substance Evaluation Conclusion document. Available at the link https://echa.europa.eu/information-on-chemicals/evaluation/community-rolling-action-plan/corap-table/-/dislist/details/0b0236e1807e66a5

ANNEXES:

Annex 1 The Background Document (BD) gives the detailed scientific grounds for the opinion. The BD is based on the CLH report prepared by the DS; the evaluation performed by RAC is contained in 'RAC boxes'.

Annex 2 Comments received on the CLH report, response to comments provided by the DS and RAC (excluding confidential information).