Committee for Risk Assessment

RAC

Annex 2

Response to comments document (RCOM)

to the 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

COMMENTS AND RESPONSE TO COMMENTS ON CLH: PROPOSAL AND JUSTIFICATION

Comments provided during public consultation are made available in the table below as submitted through the web form. Any attachments received are referred to in this table and listed underneath, or have been copied directly into the table.

All comments and attachments including confidential information received during the public consultation have been provided in full to the dossier submitter (Member State Competent Authority), the Committees and to the European Commission. Non-confidential attachments that have not been copied into the table directly are published after the public consultation and are also published together with the opinion (after adoption) on ECHA's website. Dossier submitters who are manufacturers, importers or downstream users, will only receive the comments and non-confidential attachments, and not the confidential information received from other parties.

ECHA accepts no responsibility or liability for the content of this table.

Substance name: maleic anhydride
CAS number: 108-31-6
EC number: 203-571-6
Dossier submitter: Austria

GENERAL COMMENTS

Date	Country	Organisation	Type of Organisation	Comment number
14.12.2015	United Kingdom		Company-Manufacturer	1
Comment received				
According to the consultation information, we see that the use of Maleic Anhydride (MAH) as a monomer is considered, though it seems the only polymers that are mentioned are polyester resins. Resins such as polyethylene, linear low density polyethylene, polypropylene, polyvinyl acrylates, polybutyl acrylates and polymethyl acrylates should also be considered, or at least there existence acknowledged, during any assessments. We are aware of MAH incorporated polymers with these 6 base resins being currently produced or in the development stages. In these types of products, analysis of the residual, unreacted MAH, both in the product and how much is released into the environment, has been found to be low as stated on our SDS. Additional information can be provided on request if required.				
Dossier Submitter's Response				
Thank you for this information. For the description of uses in the CLH dossier the information given in the registration dossiers has been used. It would be highly welcome if the information given above would also be reflected in the registration dossiers. It is not directly relevant for the current classification proposal but should be considered for further actions on maleic anhydride if appropriate.				
RAC's response				
Noted.				

Date	Country	Organisation	Type of Organisation	Comment number
22.01.2016	Netherlands		MemberState	2
Comment received				
• NL agrees with classification for skin sensitization, Category 1A, but proposes to add a SCL of 0.001%				

• NL agrees with retaining the classification for respiratory sensitization, though noticed that a justification for 'no sub-classification' for this endpoint is missing, nor an evaluation of the data is presented • NL disagrees with two classifications for STOT RE and instead proposes classification as STOT RE 1, H372 • NL suggests additional discussion on the inclusion of kidney effects after repeated exposure
Dossier Submitter's Response
See comment Number 9 See comment number 4 See comment number 13
RAC's response
The RAC agrees with also setting a SCL for skin sensitisation. RAC supports the STOT RE1 proposed by the DS for effects on the respiratory system, but agrees with the NL that additional classification with STOT RE2 for oral effects is not warranted. RAC also notes the lack of data in the CLH report for respiratory sensitisation, but also appreciates having some such data added by the DS to this RCOM-document.

Date	Country	Organisation	Type of Organisation	Comment number
25.01.2016	Germany		MemberState	3
Comment received				
The German CA supports the proposed classification maleic anhydride with the exception of the proposal to classify maleic anhydride as STOT RE 2 (kidney). The test results demonstrate that maleic anhydride is acutely toxic by the oral route and possesses corrosive and sensitizing potential. Maleic anhydride is classified as Skin. Corr. 1B. Therefore the proposed supplementary labelling with EUH071 (Corrosive to the respiratory tract.) is supported.				
Dossier Submitter's Response				
See comment number 14				
RAC's response				
RAC agrees with the comments above.				

RESPIRATORY SENSITISATION

Date	Country	Organisation	Type of Organisation	Comment number
25.01.2016	France		MemberState	4
Comment received				
page 34: The data used to justify classification of maleic anhydride as Resp. Sens. 1 (H334) are not provided. It is therefore not possible to consider if data are sufficient for sub-categorisation 1A or 1B.				
Dossier Submitter's Response				
The available studies on respiratory sensitisation have been assessed in the course of a substance evaluation. One animal study and observational studies (humans) have been submitted via registration. No further studies are available in open literature. The animal study is presented in the following table.				

Table 1: Animal study on respiratory sensitisation.

Method	Results	Remarks	Reference
Species: rat (Sprague-Dawley) male/female Induction: inhalation Challenge: inhalation 10m+10f per group (exposed/challenged, non-exposed/challenged, non-exposed/non-challenged) 500µg/m^3 6 hours/day for five days. Following a 3-week rest period, the animals were challenged for 6 hours (500µg/m^3) One group was not challenged (i.e., nonexposed/nonchallenged control).	sensitising The maleic anhydride-exposed/maleic anhydride-challenged animals had small, but statistically significant ($p < 0.05$), increases in maleic anhydride-specific serum IgG antibody compared to the controls (challenged and nonchallenged; females higher than males). Two rats of the MA-exposed/nonchallenged group had more than 10 lung foci (i.e., positive response); however, mean values for lung foci, weight, and volume were not significantly different from control values. Microscopic lung lesions were minimal and provided no evidence of pulmonary sensitization.	2 (reliable with restrictions) key study experimental result Test material (EC name): maleic anhydride	Amoco Corporation (1991)

There are no formally recognised and validated animal tests for respiratory sensitisation available. Maleic anhydride has been tested for potential respiratory sensitization in Sprague Dawley rats. The animals were exposed to a particulate aerosol target concentration of 0 or 500 µg/m3 maleic anhydride, 6 hours/day for five days. After three weeks, the animals were challenged with 500 µg/m^3 for 6 hours. The analytical time weighted averaged concentration of maleic anhydride was 500 and 317 µg/m^3, for the induction and challenge phases, respectively.
Maleic anhydride exposed and challenged rats had a slight, but significant, increase in maleic anhydride-specific serum IgG antibody levels compared to non-exposed control animals. Other endpoints of acid anhydride respiratory sensitization reactions in the rat model such as increased hemorrhagic lung foci, increased lung weight and volume, and extensive lung pathology did not occur (Amoco Cooperation, 1991).

Several human studies are available, which are taken into consideration to characterise the respiratory sensitisation hazard of maleic anhydride and/or acid anhydrides (see Table 2).

Table 2: Exposure-related observations on respiratory sensitisation in humans

Method	Results	Remarks	Reference
Study type: in vitro study (RAST) Type of population: occupational n=1	Conjugation of the anhydride (hapten) with human serum albumin (HSA): maleic anhydride is the simplest of the	2 (reliable with restrictions) weight of evidence	Topping M.D. et al. (1986)

	1 patient (maleic anhydride exposure) with work related respiratory symptoms	anhydrides but reacts with lysine in the same way as the other anhydrides If the antibody were primarily directed toward altered albumin, positive direct RAST results would be obtained with all sera to MA-HSA, and MA-HSA would inhibit binding to sensitizing anhydride albumin conjugate discs. The finding that this does not occur, even though a patient with occupational respiratory symptoms associated with Maleic Anhydride exposure gave a positive RAST to MA-HSA, strengthens the evidence for the involvement of the anhydride in the antibody combining site.	Test material (EC name): maleic anhydride		
	Study type: cohort study Type of population: occupational cohort of 506 workers exposed to acid anhydrides (AA): phthalic (PA), maleic (MA), and trimellitic anhydride (TMA) Prick test	Questionaire information was obtained from 401 (79%) workers. Thirty four (8.8%) had new work related respiratory symptoms that occurred for the first time while working with acid anhydrides and 12 (3.2%) were sensitised, with an immediate skin prick test reaction to AA-HSA conjugates. Sensitisation to acid anhydrides was associated with work related respiratory symptoms and with smoking at the time of exposure to acid anhydride.	2 (reliable with restrictions) weight of evidence Test material (EC name): maleic anhydride	Barker R.D. et al. (1998)	
	Study type: case report n=4	Inhalation challenge tests: a late asthmatic reaction and increased responsiveness to	4 (not assignable) weight of evidence	Graneek, B. J. et al (1986)	

	histamine following inhalation challenge to maleic anhydride in 3 out of 4 workers; IgE specific antibodies in serum equivocal results.	Test material (EC name): maleic anhydride		
Study type: case report n=2	Bronchial challenge tests: Both subjects showed immediate and late asthmatic responses to maleic anhydride challenge, observed as reductions in FEV1and an increased responsiveness to histamine at 3 and 24 hours post-challenge.	4 (not assignable) weight of evidence Test material (EC name): maleic anhydride	Graneek, B. J. et al (1987)	
Study type: case report n=1	Bronchial challenge test (34 year, man, smoker): maleic anhydride provoked immediate and last asthmatic responses; the immediate response was accompanied by rhinitis and lacrimation.	4 (not assignable) weight of evidence Test material (EC name): maleic anhydride	Lee, H.S. et al (1991)	
Occupational exposure limit (HSE)	Long term exposure limit (8-h TWA reference period): 1 mg/m3 Short term exposure limit (15-min reference period): 3 mg/m3 Sensitising	2 (reliable with restrictions) weight of evidence Test material (EC name): maleic anhydride	Ridgway P. et al. (1996)	

The studies of Graneek, B. J. et al (1986), Graneek, B. J. et al (1987), Lee, H.S. et al (1991) and Ridgway P. et al. (1996) cannot be evaluated in detail as the original literature is not available. Evaluation has been done on the information presented in the CSR and in the OECD SIDS report (OECD, 2004).

In the study of Topping et al. (1986) sera from patients sensitized to one of four acid anhydrides (TMA, PA, TCPA, MA) were studied by in virto RAST (radioallergosorbent) (direct RAST, RAST inhibition). Specific IgE antibodies to a maleic anhydride-human serum albumin conjugate from a worker that was occupationally exposed by inhalation to maleic anhydride could be detected. It was found that the anhydride is involved in the antibody-binding site.

The cohort study of Barker et al. (1998) aims to clarify risk factors for sensitisation and respiratory symptoms among workers exposed to different acid anhydrides (AA). From the cohort (out of 506 worker from 79% information was obtained) 3.2% were sensitised with an immediate skin prick test reaction to acid anhydride human serum albumin (AA-HAS) conjugate and 8.8% had new work related respiratory symptoms. Sensitisation to acid anhydrides was associated with work related respiratory symptoms and with smoking at the time of exposure to acid anhydride. When all subjects were included and all three acid anhydrides were taken into account there was no consistent evidence for an exposure-response relation, but with the analysis restricted to a factory where only trimellitic anhydride was in use, there was an increased prevalence of sensitisation to acid anhydrides and work related respiratory symptoms with increasing full shift exposure. In summary, the intensity of exposure and cigarette smoking may be risk factors for sensitisation to acid anhydrides. But, no clear prevalence of sensitised workers attributed to maleic anhydride exposure is presented in the paper, and the workers were not only exposed to maleic anhydride but also to phthalic and trimellitic anhydride. Therefore, it is not possible to clarify the skin sensitising and/or respiratory sensitizing potential of maleic anhydride exposure alone in the presented study.

Graneek et al. (1986) reported on four cases of asthma in workers exposed to maleic anhydride. No clinical or exposure histories were presented. Late asthmatic reaction and increased responsiveness to histamine following inhalation challenge to maleic anhydride were present in three of the workers. One patient had maleic anhydride-specific IgE antibodies present in the serum; these were in low titer and it was hypothesised that there may have been a cross reaction to IgE specific for trimellitic anhydride, to which this individual was also exposed to, and to which an immediate response only occurred in an inhalation challenge. The fourth worker, although negative in inhalation testing, had specific serum IgE antibodies present (cited in OECD SIDS, 2004).
The study reported by the publication of Graneek et al., 1987 airway responsiveness of two workers who suffered from work-related asthmatic symptoms associated with maleic anhydride, was investigated by bronchial challenge tests. Both subjects were declared as atopic, however clinical or exposure histories were not described. The study subjects were exposed to 5-minute inhalation to maleic anhydride dust (produced by tipping a powder containing 0.2 or 1% maleic anhydride in lactose). A control was also conducted involving exposure to lactose powder. Both subjects showed immediate and late asthmatic responses to maleic anhydride challenge, observed as reductions in forced expiratory volume and an increased responsiveness to histamine at 3 and 24 hours post-challenge.
In a case report study by Lee et al. (1991) a 34-year old man developed a cough, rhinitis, breathlessness and wheezing approximately one month after beginning working in a factory producing alkyd-polyester. The symptoms occurred within minutes of exposure to dust during the loading of chemicals into a reactor. After removal from exposure, a complete relief was observed. New exposure led to an acute asthmatic attack again. Breathing zone sampling (duration of sampling not stated) indicated airborne dust concentrations of maleic anhydride 0.8 mg/m3 (0.2 ppm) for inhalable particles and 0.2 mg/m3 (0.05 ppm) for respirable particles; equivalent concentrations for phthalic anhydride were 1.4 and 0.3 mg/m3 (0.23 and 0.05 ppm), respectively. Bronchial challenge tests were performed with phthalic anhydride and maleic anhydride. A control challenge was conducted using lactose. Maleic anhydride provoked immediate and last asthmatic responses; the immediate response was accompanied by rhinitis and lacrimation. Phthalic anhydride elicited no response. The worker also had non-specific airway hyperresponsiveness, assessed by histamine challenge (it was not stated if this hyperresponsiveness was observed in conjunction with anhydride challenge).

The HSE criteria document for an occupational exposure limit (Ridgway et al., 1996) analysed that reported adverse effects of maleic anhydride exposure are limited to a small number of cases of asthrna. Cases of work-related asthma in which bronchial challenge testing clearly demonstrated that maleic anhydride was a causal agent have been published. It is not possible with the available data to estimate the prevalence of work-related asthrna in maleic anhydride exposed workers or to draw any conclusions with respect to the concentrations necessary for the development of asthma. However, the fact that there are so few pubiished cases suggests that maleic anhydtide provokes asthma in a relatively small proportion of exposed workers. During manufacturing 97% of exposures were below 1 $mg.m^{-3}$, however this is no longer carried out in the UK. Exposure data provided by a paint and resin manufacturer´s trade association show an average task exposure of 0.12 $mg.m^{-3}$ with a maximum of 0.78 $mg.m^{-3}$. In view of this data a MEL of 1 $mg.m^{-3}$ is proposed.

The available human data support the harmonised classification of maleic anhydride as Resp. Sens. 1 according to the Regulation (EC) No 1272/2008. A subcategorisation cannot be proposed based on the available dataset.

Literature:

Amoco Corporation (1991). Respiratory sensitization study of maleic anhydride: a research project. TSCAT, 86-920000056, OTS 0533622; cited in OECD SIDS for CAS. Nos. 108-31-8/ 110-16-7, 2004. Testing laboratory: IITS Research Institute. Owner company: Amoco Corporation. Study number: 1277C. Report date: 1991-09-30.

Barker R. D. et al. (1998). Risk factors for sensitisation and respiratory symptoms among workers exposed to acid anhydrides: a cohort study. Occup Environ Med 1998; 55:684–691.

Graneek, B. J., Durham, S. R., and Newman-Taylor, A. J. (1987) Late asthmatic reactions and changes in histamine responsiveness provoked by occupational agents. Clin. Respir. Physiol. 23: 577-581. cited in OECD SIDS Draft for CAS. Nos. 108-31-8/ 110-16-7, 2004.

Graneek, B. J., Durham, S. R., Topping, M., Tee, R. D., Hawkins, R., and Newman-Taylor, A. J. (1986) Occupational exposure caused by maleic anhydride: bronchial provocation testing and immunologic data. Thorax 41: 251 [abstract] cited in OECD SIDS Draft for CAS. Nos. 108-31-8/ 110-16-7, 2004.

Lee, H. S., Wang, Y. T., Cheong, T. H., Tan, K. T., Chee, B. E., and Narendran, K. (1991) Occupational asthma due to maleic anhydride. Br. J. Industr. Med. 48: 283-285. cited in OECD SIDS Draft for CAS. Nos. 108-31-8/ 110-16-7, 2004.

Ridgway P. et al. (1996). ACID ANHYDRIDES Criteria document for an occupational exposure limit. HSE books, 1996.

Topping, M. D., Venables, K. M., Luczynska, C. M., Howe, W., and Newman-Taylor, A. J. (1986). Specificity of the human igE response to inhaled acid anhydrides. J. Allergy and Clinical Immunol. 77: 834-843.

RAC's response

Thanks for the additional information. Slightly increased titers of IgG in rats exposed to maleic anhydride via inhalation, and a few human case reports where inhalation challenge tests with maleic anhydride have led to respiratory problems support respiratory sensitisation. We agree that sub-categorisation based on this data seems very difficult.

Date	Country	Organisation	Type of Organisation	Comment number
22.01.2016	Netherlands		MemberState	5

Comment received

The classification of maleic anhydride was already discussed in 1998 and it was concluded at that time that the compound should be classified for respiratory sensitization.

According to the current CLP-criteria, sub-classification should be taken into account for this endpoint. The dossier submitter states that the previous classification is justified and proposes no sub-classification. However, no evaluation of the data is presented and the justification for this conclusion is missing. If the endpoint was not re-evaluated, this should be stated more clearly. Otherwise, at least the respiratory sensitization study provided in the substance registration dossier should be included in the evaluation of this endpoint. Also some of the human cases included under respiratory irritation seem relevant for respiratory sensitization and should be included in this discussion.
Dossier Submitter's Response
See previous comment (number 4).
RAC's response
Noted.

Date	Country	Organisation	Type of Organisation	Comment number
25.01.2016	Sweden		MemberState	6
Comment received				
This endpoint is open for commenting, but no data from studies on respiratory sensitisation for maleic anhydride is provided in the CLH report. For transparency – please provide data from studies and justification for this proposal.				
Dossier Submitter's Response				
See comment number 4.				
RAC's response				
Noted. RAC also notes the lack of data in the CLH report for respiratory sensitisation, but also appreciates having some such data added by the DS to this RCOM-document. See above (comment number 4).				

OTHER HAZARDS AND ENDPOINTS – Acute Toxicity

Date	Country	Organisation	Type of Organisation	Comment number
25.01.2016	Germany		MemberState	7
Comment received				
Maleic anhydride meets the criteria for classification and labelling for acute oral toxicity as Acute Tox. 4; H312 according to CLP.				
Dossier Submitter's Response				
We think the comment supports classification for Acute Tox 4, H302 (typing error?) Harmful if swallowed. Acute dermal toxicity (corresponding to H312) was not evaluated in this CLH dossier. During substance evaluation available data was evaluated (LD50=2620 mg/kg) and no classification was indicated.				
RAC's response				
The present acute tox 4 classification for the oral route seems clear-cut, and the removal of the asterix is supported. Some data on acute toxicity via the inhalation route is presented in the CLH report in relation to STOT RE, but the transparency would have been increased by also presenting it under the heading of acute toxicity.				

OTHER HAZARDS AND ENDPOINTS – Eye Hazard

Date	Country	Organisation	Type of Organisation	Comment number
25.01.2016	Germany		MemberState	8

Comment received
The available data on eye effects of maleic anhydride fulfil the criteria for Eye Dam. 1; H318 (Causes serious eye damage).
Dossier Submitter's Response
Thank you for this support.
RAC's response
The support is noted.

OTHER HAZARDS AND ENDPOINTS – Skin Sensitisation Hazard

Date	Country	Organisation	Type of Organisation	Comment number
22.01.2016	Netherlands		MemberState	9
Comment received				
We agree with the proposed classification in Category 1A. However, the EC3 value from the LLNA of 0.16% is below the limit of 0.2% for extreme sensitisers, as defined in the CLP guidance (version 4.1, 2015). The sensitizing potential of maleic anhydride is further supported by the findings in a Buehler test (maleic anhydride tested as a mixture in mineral oil) and by human data, although these studies do not allow the derivation of a concentration limit. Considering the extreme sensitizing potential, we would like to propose a SCL for skin sensitization of 0.001%.				
Dossier Submitter's Response				
Thank you for this remark. The LLNA assay demonstrates a EC3 value ≤ 2 % and the Buehler test indicates that ≥ 60 % of test animals responds at > 0,2 % to ≤ 20 % topical induction dose, which indicates that maleic anhydride is a strong to extreme skin sensitizer. Furthermore, human data confirm the results obtained from animal experiments of maleic anhydride being a skin sensitiser. According to CLP guidance, Chapter 3.4.2.2.5, the setting of SCL is based on potency. SCL generally applies for the most potent skin sensitisers classified in 1A. The GCL of components of a mixture classified as either respiratory sensitisers or skin sensitisers that trigger classification of the mixture in Sub-category 1A is ≥ 0,1%. If the GCL may not be sufficiently protective then an SCL shall be set in accordance with CLP Article 10, which will better reflects the hazard of mixtures containing that skin sensitiser. According to CLP guidance for sensitizers with extreme potency a SCL is recommended. Based on this guidance for maleic acid a SCL of ≥0.001 (% w/v) for Skin Sens 1A is proposed.				
RAC's response				
The RAC notes the extreme potency, and supports a SCL of 0.001%.				

Date	Country	Organisation	Type of Organisation	Comment number
25.01.2016	Sweden		MemberState	10
Comment received				
The outcome of two animal studies with high reliability (LLNA + Buehler) shows that maleic anhydride has skin sensitizing properties (EC3 value of 0.16% + 100% of animals sensitised at a topical induction dose of 5%). These animal studies are further supported by human evidence of skin sensitisation. An EC3 value of ≤ 2% (LLNA) and a frequency of ≥60% of test animals responding positively at >0.2% to ≤ 20% topical induction dose (Buehler) warrants classification in subcategory 1A. The Swedish CA supports classification of maleic anhydride as Skin Sens. 1A, and suggests setting a SCL of 0.001% due to the extreme potency of the substance in the LLNA assay (EC3 value ≤ 0.2%).				

Dossier Submitter's Response
See comment above (number 9).
RAC's response
Noted. See above.

Date	Country	Organisation	Type of Organisation	Comment number
25.01.2016	Germany		MemberState	11
Comment received				
Maleic anhydride has shown clear evidence of skin sensitization in mice (LLNA) and guinea pigs (Buehler Test). In addition case reports and cohort studies have demonstrated that maleic anhydride possess skin sensitizing potential. In accordance with the given criteria for sub-categories for skin sensitization, maleic anhydride fulfils the criteria for classification as skin sensitizer sub-category 1A (H317: May cause an allergic skin reaction).				
Dossier Submitter's Response				
Thank you for this support.				
RAC's response				
The support is noted.				

OTHER HAZARDS AND ENDPOINTS – Specific Target Organ Toxicity Repeated Exposure

Date	Country	Organisation	Type of Organisation	Comment number
17.12.2015	Slovenia	BENS consulting s.o.o.	Company-Importer	12
Comment received				
Proposed classification for maleic anhydride that was made by 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) is STOT RE 1, H372 (respiratory system) and STOT RE 2, H373 (kidney). According to classification criteria for STOT RE (section 3.9.2.1 , ANNEX I, Regulation 1272/2008), substance classified as specific target organ toxicants following repeated exposure should be placed in one of two categories, depending upon the nature and severity of the effect(s) observed. Furthermore, Guidance on the Application of the CLP Criteria (p. 466, Version 4.1 – June 2015) explains this rule even clearer; If the data show that classification is warranted in Category 1 for one route and in Category 2 for another route then the substance shall only be classified in Category 1. Proposed classification disregarded this rule and classified maleic anhydride in both STOT RE categories. That is why, we propose correction of classification to only STOT RE 1, H372 (respiratory system, kidney).				
Dossier Submitter's Response				
We agree that it should be covered in STOT RE1, H372 (respiratory system, kidney) in case both endpoints are included.				
RAC's response				
RAC agrees in general with the comment, but we do not think the the effects on kidney warrants classification, thus the RAC proposes classification with STOT RE1 (respiratory system).				

Date	Country	Organisation	Type of Organisation	Comment number
22.01.2016	Netherlands		MemberState	13

Comment received

The proposal is for classification in Category 1 for the route inhalation (respiratory tract) and Category 2 for oral exposure (kidney). However, according to the CLP guidance, 'If the data show that classification is warranted in Category 1 for one route and in Category 2 for another route then the substance shall only be classified in Category 1'. In addition paragraph 3.9.2.1 of the criteria states that substances are placed in one of two categories. Thus, we propose to classify maleic anhydride as STOT RE 1, H372.

The available repeated dose inhalation studies show that Category 1 is justified for the route inhalation (respiratory tract). Effective dose levels are well below the upper limit for STOT RE1 classification and further, the type of effects indicate significant organ damage and marked organ dysfunction. The effects are probably related to the corrosive properties of the compound for which it can be questioned whether this is a repeated or an acute effect. However, given the large difference between the effective concentrations in the 28-d repeated dose toxicity study (≥0.012 mg/l/6h/d) and the acute effect level (based on a converted 4-h LC50 of >1.08 mg/l from a multispecies acute inhalation toxicity study with one exposure concentration applied), we agree that the observed effects on the respiratory tract can be considered the result of repeated exposure. Thus, we agree with classification of maleic anhydride as STOT RE 1, H372, with the respiratory system as target organ.

Regarding the kidney toxicity observed in several oral rat studies, we think further discussion is necessary on whether the effects are sufficiently severe and relevant to warrant the addition of the kidney as target organ, as most effects observed occurred above the guideline values. We would like to pose the following questions for further discussion:
- Adverse effects on the kidneys at or below the guideline value for STOT RE 2 were found in a 90-day study (Humiston et al 1975) and a 2-generation study (Short 1982). In the 90-day study, the effects at 100 mg/kg/day were renal tubular dilatation hypertrophy, degeneration of the tubular cells in the cortical portion of the nephron in 5 out of 15 male rats. In the 2-gen study, several changes were observed, which were stated to be randomly distributed over the dose groups. Could you provide more specific information on this study, in particular the incidence and severity of the kidney effects in the low dose group (20 mg/kg bw/day)?
- It is noted that males were more sensitive to kidney toxicity than females and that the kidney effects were not reproducible in dogs. Has α2u-globulin-associated nephropathy been considered as a possible mode of action and/or has α2u-globulin been determined in any of the studies? If the nephrotoxicity is indeed α2u-globulin-associated, the observed kidney toxicity in rats is not relevant for humans. (See for more details on α2u-globulin-associated nephropathy section 3.9.2.5.3. of the CLP guidance or "Factsheets for the (eco)toxicological risk assessment strategy of the National Institute for Public Health and the Environment (RIVM), Part II")

Dossier Submitter's Response

We agree that the single target organ toxicity of maleic anhydride should be covered in STOT RE1, H372 (respiratory system, kidney) in case both endpoints are included (see discussion below).

Thank you for the support on STOT RE 1, H372.

We are aware that effects on the kidneys are a matter of discussion. Unfortunately no individual animal data from the study Short, 1982 was available before submission of the

CLH dossier. Meanwhile industry has provided the full study report and more detailed information (pathology - individual animal data) has been prepared and attached to this document (confidential Annex I).

Considerations concerning α2u-globulin-associated nephropathy

- No protein droplet accumulation is described in the histolog. examination by Short, 1982 and Humiston, 1975.
- Study by Short, 1982 show effects in females as well
- α2u-globulin been not determined in any of the studies
- the available carconigenicity study (registration data, Procter & Gamble Company, 1983) (126 Fische 344 rats/sex/group exposed to 0, 10, 32, or 100 mg/kg/day maleic anhydride in feed, seven days a week for two years, NOEL (carcinogenicity) >=100mg/kg bw) gives no evidence of a possible α2u-globulin-associated mechanism.

α2u-globulin-associated nephropathy does not seem to be the mode of action.

ECHA note: An attachment was submitted with the comment above. Refer to confidential attachment CLH_RCOM_ATT_CONF_AT_EG012271-67.

RAC's response

The support for STOT RE1 is noted. Regarding the kidney findings in the 2-generation study by Short et al (1982), the RAC is of the opinion that adverse kidney effects only were observed in FO animals of the top dose (150 mg/kg/day). However, it should be noted that 20 out of 30 animals died at this dose. Pneumonia and/or septicaemia was observed in 16 of the dead animals, and in many cases being the cause of death. In 11 animals, kidney toxicity was given as cause of death, but only two of these cases occurred in the absence of pneumonia/septicaemia. Many animals also had stomach imflammation, sometimes in combination with stomach ulcers. Overall, there seems to be many reasons for the high lethality at this dose, making it difficult to use the results in a meaningful way. Since no F1 females survived at the dose of 150 mg/kg/day, this dose clearly exceeds the MTD in female rats and the kidney findings can therefore be considered of no relevance in relation to classification.

Date	Country	Organisation	Type of Organisation	Comment number
25.01.2016	Germany		MemberState	14

Comment received

STOT RE 1 Respiratory System

The results of a sub-acute inhalation toxicity study with rats and a multispecies study have demonstrated repeated dose toxicity findings relevant for classification of maleic anhydride as STOT RE 1 (H372: Causes damage to the respiratory tract through prolonged or repeated exposure). Furthermore the label with EUH071 (Corrosive to the respiratory tract) is necessary according to Annex II, 1.2.6. ('For substances and mixtures in addition to classification for skin corrosivity, if no acute inhalation test data are available and which may be inhaled.').

Comment

In the CLH report on page 54 an acute inhalative multispecies toxicity study is mentioned (BASF, 1953). In paragraph 3 is stated: "Five (4 mice and 1 guinea pig) out of 17 animals died attributed to inhalative exposure to maleic anhydride (1 hour, 4.35 mg/l) at day 6 and day 8 after exposure."

This information is inconsistent with information given on the ECHA website referring to

this study, where 1/1 guinea pig died after 8 days and 2/10 mice died after 8 days. How many mice died and when? Please check and clarify.

STOT RE 2 Kidney
The kidney effects caused by maleic anhydride do not suggest classification for target organ toxicity from a repeated exposure. There is no doubt that maleic anhydride produces effects on kidneys of rats. The effects of maleic anhydride on the kidneys in rats observed after repeated exposure by the oral route should be considered as 'adverse' at the high dose levels tested. However, findings judged as toxicologically significant toxic effects according to CLP criteria were observed in male and female rats after repeated oral administration of 150 mg/kg bw/d maleic anhydride in a two-generation toxicity study (OECD TG 416) and at the highest dose of 600 mg/kg bw/d tested in a sub-chronic toxicity (90-day) study (OECD TG 408). The effects of maleic anhydride observed from both toxicity studies at dose levels approximately equal to the STOT RE 2 cut offs according to CLP (Annex I, Part 3, guidance value: oral (rat): 10 < C ≤ 100 mg/kg bw/d) are not significant toxic effects according to CLP criteria. Furthermore no relevant toxic effects to maleic anhydride, in particular with regard to kidney effects, were noted in a sub-chronic toxicity study with Beagle dogs (OECD TG 409) at the highest dose tested of 60 mg/kg bw/d and in a chronic toxicity study (OECD TG 452) in rats after administration of 100 mg/kg bw/d for two years.
Based on the available data, we are of the opinion that maleic anhydride does not fulfil the criteria for classification for target organ toxicity through repeated exposure, STOT RE 2, H373 (May cause damage to the kidneys through prolonged or repeated exposure). It is suggested not to classify maleic anhydride for STOT RE 2 (kidney).

Remarks
o In the key study of Humiston 1975 the LOAEL (male) for renal changes is right at the upper value of the guidance value of 100 mg/kg bw/day. Nevertheless, it refers to minimal/mild renal changes (renal tubular dilatation hypertrophy, degeneration of the tubular cells in the cortical portion of the nephron) in 5/15 animals. The effects were not significant at this dose level (CLH report: page 43 and table 2 in Annex II).
o One supporting study (Braun 1975) determined no relevant effects up to the highest examined dose in Beagle dogs.
o Relevant results of two other supporting studies (Humiston 1977 and Procter & Gamble 1983) were observed only at doses that exceeded the relevant guidance values for classification with STOT RE 2 as laid down in the CLP regulation (table 3.9.3. page 181) by around/more than 2,5-fold.
o The CLH report states that the supporting study of Short et al. 1982 (Short et al. 1982 was published in Short et al. 1986 according to literature reference list of the CLH-report) observed "compound related changes in the kidneys of rats". However, these were found only in the highest dose group and thereby do not support classification.
o The values of the observed significantly increased absolute kidney weights in F1-females (study: Short et al. 1982) from the low- and mid-dose group were missing in the CLH-report. They are 108% and 111% respectively.

Please clarify:
o In the supporting study of Short et al. 1982 (Short et al. 1982 was published in Short et al. 1986 according to literature reference list of the CLH-report) the LOAEL for systemic effects in the F0/F1 generation is given in the CLH-report with 20 mg/kg bw/day and is therefore within the derived guidance value range of 4,3 <c ≤ 43 mg/kg bw/day for a 2-generation study with a duration of around 210 days.
o However, it remains unclear on what ground this LOAEL was set since the contents of the following statements from the CLH report were not found in the original publication of Short et al. 1986 (where Short et al. 1982 is published in according to the reference list):

o "For animals in the F0 generation, toxicologically significant changes observed during post-mortem examination included hydronephrosis/dilated pelvis, kidneys with a mottled appearance or irregular surface and calculi in the urinary bladder. These lesions were randomly distributed among males/females in 20, 55, 100 mg/kg bw/day dosage group."
o "Other compound related changes included hydronephrosis, chronic pyelonephritis, nephrosis, inflammation of the urinary bladder and urinary calculi. Changes were randomly distributed among animals in all dosage groups. The changes to the kidney are attributed to the maleic anhydride exposure."
o The word "bladder" was not found in the publication of Short et al. 1982 (in Short et al. 1986).
o The conclusion "The study author conclude that, dose levels of 150 mg/kg/day and less were observed to produce morphological changes in the kidney and bladder of F0 parents with similar albeit equivocal findings in F1 parents." was not extractable from the mentioned publication of Short et al. 1982 (in Short et al. 1986).

Dossier Submitter's Response

(1) Thank you for the support on STOT RE 1, H372.

(2) Additional labelling as EUH071 (Corrosive to the respiratory tract) is indicated (according to CLP regulation, Annex II).

(3) Clarification regarding the information from BASF, 1953:
The information on this acute toxicity study is very limited. Animals were exposed to maleic anhydride atmosphere of 4.35 mg/L for one hour The results are shown in the following table:

Animal	Symptoms
Cat (1)	Lacrimation after 2min, redness of conjunctiva at the end of the study
Rabbit (1)	Wiping of the snoute after 2min, redness of conjunctiva at the end of the study
Guinea pig (1)	No symptoms during exposure, death at day 8 (pneumonia)
Rats (4)	No symptoms
Mice (10)	No symptoms during exposure, 2 mice died respectively at day 6 and 8

The information given in the CLH report is correct:
"Five (4 mice and 1 guinea pig) out of 17 animals died attributed to inhalative exposure to maleic anhydride (1 hour, 4.35 mg/l) at day 6 and day 8 after exposure."

(4) STOT RE2 kidney
We are aware that the classification for kidney toxicity is a boarderline case. Nevertheless there is a clear trend for kidney toxicity of maleic anhydride.

For clarification:
The study by Short, 1982 is a confidential, good elaborated study and the data were partly published by Short et al, 1986 in an official journal. Short, 1982 was provided by industry and includes more detailed information. We suggest to include a remark concerning this matter in the references to avoid any confusion:

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. 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.

The above questioned statements are therefore correct (Short, 1982) but are not to be found in the official journal (Short, 1986):
"For animals in the F0 generation, toxicologically significant changes observed during post-mortem examination included hydronephrosis/dilated pelvis, kidneys with a mottled appearance or irregular surface and calculi in the urinary bladder. These lesions were randomly distributed among males/females in 20, 55, 100 mg/kg bw/day dosage group." …"Other compound related changes included hydronephrosis, chronic pyelonephritis, nephrosis, inflammation of the urinary bladder and urinary calculi. Changes were randomly distributed among animals in all dosage groups. The changes to the kidney are attributed to the maleic anhydride exposure (Short, 1982).

It is correct that the bladder is not mentioned in the publication by Short, 1986 but it was examined and documented in the original not public available data (Short, 1982).
It is therefore correct that the study author conclude that, dose levels of 150 mg/kg/day and less were observed to produce morphological changes in the kidney and bladder of F0 parents with similar albeit equivocal findings in F1 parents." (Short, 1982)

For further details on kidney/bladder effects in the study by Short, 1982 see confidential Annex I to this document.

ECHA note: An attachment was submitted with the comment above. Refer to confidential attachment CLH_RCOM_ATT_CONF_AT_EG012271-67.

RAC's response

The support for STOT RE1 and EUH071 is noted and agreed. Regarding the kidney findings in the 2-generation study by Short et al (1982), please see the response to comment number 13.

CONFIDENTIAL ATTACHMENTS

1. CLH_RCOM_ATT_CONF_AT_EG012271-67. [Please refer to comment No. 14]