OPINION OF THE MEMBER STATE COMMITTEE

ON THE IDENTIFICATION OF

BENZENE-1,2,4-TRICARBOXYLIC ACID 1,2-ANHYDRIDE

AS A SUBSTANCE OF VERY HIGH CONCERN

According to Articles 57 and 59 of
Regulation (EC) 1907/2006[1]

Adopted on 15 December 2016

This opinion concerns

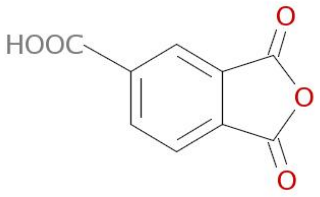
Substance name: Benzene-1,2,4-tricarboxylic acid 1,2-anhydride (TMA)

EC number: 209-008-0

CAS number: 552-30-7

Molecular formula: $C_9H_4O_5$

Structural formula:



[1]Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC

The Netherlands presented a proposal in accordance with Article 59(3) and Annex XV of the REACH Regulation (30 August 2016, submission number SPS-012443-16) on identification of *Benzene-1,2,4-tricarboxylic acid 1,2-anhydride* as a substance of very high concern due to its respiratory sensitising properties.

The Annex XV dossier was circulated to Member States on 6 September 2016 and the Annex XV report was made available to interested parties on the ECHA website on the same day according to Articles 59(3) and 59(4).

Comments were received from both Member States and interested parties on the proposal.

The dossier was referred to the Member State Committee on 22 November 2016 and was discussed in the meeting on 12-16 December 2016 of the Member State Committee.

MSC **did not reach** unanimous agreement on whether the information provided in the SVHC proposal is sufficient to constitute an equivalent level of concern to CMRs in accordance with Article 57 (f) of the REACH Regulation.

Pursuant to Articles 59 (9) and 85(8) of REACH in order for the Commission to draft a proposal on the identification of the substance in accordance with the procedure outlined in Article 133 (3) of the REACH Regulation, the Member State Committee provides this opinion, consisting of the view of the majority of its members, including its grounds.

Three MSC members expressed a minority view, including their grounds that is made available in a separate document.

In accordance with Article 59 (9), a final decision on the identification of TMA shall be taken in accordance with the procedure referred to in Article 133(3).

Opinion of the Member State Committee in accordance with Article 59(8):

Benzene-1,2,4-tricarboxylic acid 1,2-anhydride **should be identified as a substance meeting the criteria of Article 57 (f) of Regulation (EC) 1907/2006 (REACH) because it is a substance with respiratory sensitising properties for which there is scientific evidence of probable serious effects to human health which gives rise to an equivalent level of concern to those substances listed in points (a) to (e) of Article 57 REACH.**

UNDERLYING ARGUMENTATION
FOR IDENTIFICATION OF A SUBSTANCE OF VERY HIGH CONCERN

Equivalent level of concern:

Benzene-1,2,4-tricarboxylic acid 1,2-anhydride (also known as trimellitic anhydride; TMA) is covered by index number 607-097-00-4 in Annex VI, part 3 of Regulation (EC) No 1272/2008 and classified as respiratory sensitiser.

Benzene-1,2,4-tricarboxylic acid 1,2-anhydride should be identified as a substance of very high concern in accordance with Article 57(f) of Regulation (EC) 1907/2006 (REACH) because it is a substance with respiratory sensitising properties for which there is scientific evidence of probable serious effects to human health which gives rise to an equivalent level of concern to those substances listed in points (a) to (e) of Article 57 of REACH.

TMA causes serious and permanent impairment of lung functions, if the exposure is prolonged and no interventions take place. Whereas TMA-induced sensitisation is irreversible, exposure is needed to elicit the effect. For studying respiratory sensitisation, no validated animal model is available that might provide quantitative information. From the available human data, it is not possible to derive a "safe" no effect level below which sensitisation is prevented. Exposure estimates for working conditions indicate an increased risk of respiratory sensitisation due to TMA exposure, where the derived additional risk levels are below the OELs in most EU countries, i.e. lower than 40 ug/m^3 and lower than the lowest OEL in Europe, i.e. 2 ug/m^3 (TWA 15 min) in Belgium. The social impact can include retraining of affected persons, limitation of the possibility of a normal working life, and it could require long-term medication. Therefore, it is concluded that TMA fulfils the criteria of being of an equivalent level of concern as CMR substances. TMA can be regarded as a substance of very high concern (SVHC) according to Article 57(f) of the REACH legislation (Regulation (EC) No 1907/2006) and may be included in Annex XIV.

Keskinen (2004)[2], the WHO (2009) and the Dutch Health Council (2010) have written reports on cyclic anhydrides, (including TMA), describing several case studies, case reports and epidemiological studies where the respiratory sensitisation property of TMA in humans is demonstrated. The severity of the cases reported vary from occupational rhinoconjunctivitis and asthma to the severe diseases: pulmonary disease–anaemia syndrome, allergic laryngitis, and allergic alveolitis. Skin diseases as a result of sensitisation such as contact eczema, contact urticarial have also been reported.

The case reports and epidemiology studies in worker populations have shown that health effects such as rhinitis, conjunctivitis and occupational asthma can result from TMA exposure. The epidemiological studies and case studies combined included approximately 1650 workers in various industries where TMA is, or has been, used. The exposure levels to TMA ranged from <0.41 to 6500 µg/m^3. In the studies, in total 117 workers were reported to be clinically affected by TMA showing 42 occupational asthma cases, 9 pulmonary disease-anaemia cases, 4 worker with irritation symptoms, 28 with rhinitis and/or conjunctivitis (often preceding asthma cases, possible double-counting is accounted for), 1 allergic alveolitis case and 58 workers were reported with undisclosed respiratory symptoms. It is noted that these figures are possibly underestimates. Some of the effects have been so severe that subjects were forced to leave their job. It is noted that most cases date back to the period 1990-2006, cases that are more recent have not been found in the literature.

The Dutch Health Council (in 2010) evaluated the cyclic anhydrides (including

[2] More information about different studies and references to them can be found in the Support document to the MSC opinion on TMA prepared in the context of the identification of this substance as an SVHC.

TMA) to derive health-based recommended occupational exposure limits. The Dutch Health Council advised additional risk levels:

"Exposure and response data were available from an observational study with a cohort design (Grammer et al. (1999)). From the fitted dose response curve, an exposure level was calculated at which 10% of the occupationally exposed population will get specifically sensitized to TMA. This level corresponded to 18 µg TMA/m^3. This level was used as a starting point for calculating exposure levels with lower sensitizing risks, i.e. 0.1% and 1%.

Using a linear extrapolation model, the exposure levels (reference values) corresponding to an additional risk of 0.1% and 1% amount to:

- *0.18 µg TMA/m^3, which corresponds to an additional risk of 0.1% due to occupational exposure, as an 8-hour time weighted average concentration*
- *1.8 µg TMA/m^3, which corresponds to an additional risk of 1% due to occupational exposure, as an 8-hour time weighted average concentration.*

The predefined additional risks are extra risks caused by occupational exposure that comes on top of the risk of getting sensitized to TMA in the general population. The reference values serve as indicative values, and policy and social considerations should be taken into account in deciding on the level of the predefined additional risk levels. In the Netherlands, no decisions have yet been made about accepted additional response levels for allergic sensitisation of inhaled allergens".

It should be noted that above-mentioned risk levels are for sensitisation – induction only and do not protect workers whom have been sensitised previously from adverse effects. Currently, no safe level for TMA can be established for previously sensitised workers, where in practice it means that workers will have to be relocated to ensure zero exposure.

In addition, TMA has similar properties as two other cyclic anhydrides that have been identified as SVHCs (Article 57(f)) and were placed on the Candidate List after unanimous MSC agreement. Basically, the same rationale applies to TMA, as it appears that the underlying information on toxicity and uses is similar.

Rationale for 57(f) criteria:

Severity: may result in occupational rhinoconjunctivitis and asthma, less frequent consequences are the severe diseases: pulmonary disease–anaemia syndrome, allergic laryngitis, and allergic alveolitis, and skin-related disease such as contact eczema, contact urticaria.

Reversibility: sensitisation and certain (severe) effects as results of prolonged exposure are irreversible. Adaptive effects are reversible upon cessation of the exposure, but will emerge and worsen upon new contact. For structurally related respiratory sensitisers of similar potency, the Court concluded that the induction phase is irreversible and that, during the elicitation phase, even if effects on health are in principle reversible, prolonged exposure can lead to irreversible effects.

Threshold: the current data on TMA do not allow the derivation of a safe threshold.

Time to effect: for severe effects there appears to be some latency time and prolonged exposures are sometimes required dependent on the level of exposure. Effects are also observed after high acute exposure.

Other factors: societal concern and quality of life relates to the fact that occupational diseases that may arise from exposure to TMA may lead to high costs, prolonged medical treatment, job absenteeism, and re-training of the workers as even very low exposures can result in severe health effects.

In conclusion, the substance *benzene-1,2,4-tricarboxylic acid 1,2-anhydride* meets the criteria of Article 57(f) of Regulation (EC) 1907/2006 (REACH) and should be identified as a substance of very high concern because it is a substance

with respiratory sensitising properties for which there is scientific evidence of probable serious effects to human health which gives rise to an equivalent level of concern to those substances listed in points (a) to (e) of Article 57 of REACH.

Reference:

Support Document to the MSC opinion on *benzene-1,2,4-tricarboxylic acid 1,2-anhydride* (TMA) (Member State Committee, 15 December 2016)