Substance Name: Benzene-1,2,4-tricarboxylic acid 1,2-anhydride (trimellitic anhydride; TMA)

EC Number: 209-008-0

CAS Number: 552-30-7

SUPPORT DOCUMENT TO THE OPINION

OF MEMBER STATE COMMITTEE

ON THE IDENTIFICATION OF

BENZENE-1,2,4-TRICARBOXYLIC ACID 1,2-ANHYDRIDE AS A SUBSTANCE OF VERY HIGH CONCERN BECAUSE OF ITS RESPIRATORY SENSITISING PROPERTIES WHICH CAUSE PROBABLE SERIOUS EFFECTS TO HUMAN HEALTH WHICH GIVE RISE TO AN EQUIVALENT LEVEL OF CONCERN TO THOSE OF CMR[1]s AND PBTs/VPVB[2] SUBSTANCES (ARTICLE 57 F)

Adopted on 15 December 2016

[1] CMR means carcinogenic, mutagenic or toxic for reproduction

[2] PBT means persistent, bioaccumulative and toxic; vPvB means very persistent and very bioaccumulative

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TABLES

IDENTIFICATION OF A SUBSTANCE OF VERY HIGH CONCERN ON THE BASIS OF THE CRITERIA SET OUT IN REACH ARTICLE 57

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

EC Number: 209-008-0

CAS number: 552-30-7

- The substance should be identified as a substance of equivalent level of concern to those of other substances listed in points (a) to (e) of Article 57 of Regulation (EC) No 1907/2006 (REACH) according to Article 57(f) of REACH Regulation.

*Note – throughout this report the substance **benzene-1,2,4-tricarboxylic acid 1,2-anhydride** is also referred to as trimellitic anhydride and/or its abbreviation TMA.*

Summary of how the substance meets the criteria set out in Article 57 of the REACH Regulation

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 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[3]. 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), 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

[3] https://www.ser.nl/nl/grenswaarden/trimellietzuuranhydride.aspx access date April 6th 2016.

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 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 (Art. 57f) 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 57f 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[4] 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.

Conclusion: 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 REACH.

Registration dossiers submitted for the substance: Yes

[4] General Court 30 April 2015 T-134/13 on HHPA and T-135/13 on MHHPA

Justification

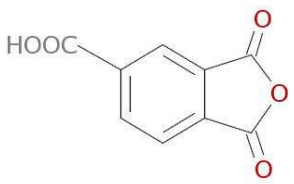
1 Identity of the substance and physical and chemical properties

1.1 Name and other identifiers of the substance

Table 1: Substance identity

EC number:	209-008-0
EC name:	Benzene-1,2,4-tricarboxylic acid 1,2-anhydride
CAS number (in the EC inventory):	552-30-7
CAS number: **Deleted CAS numbers:**	
CAS name:	5-Isobenzofurancarboxylic acid, 1,3-dihydro-1,3-dioxo-
IUPAC name:	1,3-dioxo-1,3-dihydro-2-benzofuran-5-carboxylic acid
Index number in Annex VI of the CLP Regulation	607-097-00-4
Molecular formula:	$C_9H_4O_5$
Molecular weight range:	192.125 g/mol
Synonyms:	Trimellitic anhydride, TMA, 1,3-dioxo-1,3-dihydro-2-benzofuran-5-carboxylic acid, 1,2,4-Benzenetricarboxylic acid, cyclic 1,2-anhydride, 1,2,4-Benzenetricarboxylic anhydride, 1,3-dioxo-1,3-dihydro-2-benzofuran-5-carboxylic acid, 1,3-dioxo-2-benzofuran-5-carboxylic acid, 1,3-dioxo-5-isobenzofurancarboxylic acid, 5-isobenzofurancarboxylic acid, 1,3-dihydro, 1,3-dioxo, Anhydride trimellitique, Benzen-1,2,4-trikarboxy-1,2-anhydrid, Benzene-1,2,4-tricarboxylic acid 1,2-anhydride, Trimelliticanhydride

Structural formula:



1.2 Composition of the substance

Name: Benzene-1,2,4-tricarboxylic acid 1,2-anhydride (synonym: Trimellitic anhydride)

Description:

Substance type: mono-constituent

Table 2: Constituents

Constituents	Typical concentration	Concentration range	Remarks
Trimellitic anhydride 209-008-0	≥ 80 % w/w	-	

Impurities are listed in the confidential annex II.

No additives have been reported.

1.3 Identity and composition of degradation products/metabolites relevant for the SVHC assessment

Not relevant for the identification of the substance as SVHC in accordance with Article 57 (f) of REACH.

1.4 Identity and composition of structurally related substances (used in a grouping or read-across approach)

Not relevant for the identification of the substance as SVHC in accordance with Article 57 (f) of REACH.

1.5 Physicochemical properties

Table 3: Overview of physicochemical properties as reported on the ECHA dissemination website (date August 2016).

Property	Results	
Physical state at 20°C and 101.3 kPa	Trimellitic anhydride is a solid organic substance commercially available as white to yellow flakes or tablets, with a pungent odour.	Solid.
Melting/freezing point	The melting point of trimellitic anhydride is 167.2°C.	167.2°C at 1013 hPa.
Boiling point	Trimellitic anhydride is reported to have a boiling point of 390°C.	390°C at 1013 hPa.
Relative density	The density of trimellitic anhydride, determined with a pycnometer according to CIPAC method MT 3.2 (iv) is 1.4867 g/mL at 20°C. Its specific gravity is 1.4894 at 20°C and its relative density (D20/4) is 1.4867.	1.4867 at 20°C.

Property	Results	
Vapour pressure	The vapour pressure of trimellitic anhydride (TMA) was measured using the dynamic method of gas-saturation or transpiration at temperatures ranging from 60 to 180°C, and the VP-temperature relationship based on the Clausius-Clapeyron equation used to extrapolate to temperatures below the range of measurement. The method is generally suitable for materials that are relatively non-volatile and have high boiling points and is more reliable than extrapolations based on data obtained with molten material. Extrapolated vapour pressures of TMA at 20 and 25°C were 0.0000000000682 and 0.00000000015 atm (equivalent to 0.0000069 and 0.0000152 Pa), respectively. These values are very low compared to normal atmospheric pressure.	0.0000152 Pa at 25°C.
Surface tension	In accordance with Column 2 adaptation statement of REACH Annex VII, information requirement section 7.6, this study does not need to be conducted if, based on structure, surface activity is not expected and no surface-active properties would be predicted for this compound. Surface activity is not a desired property of trimellitic anhydride (TMA) or its hydrolysis product trimellitic acid (TMLA). Consequently, a test of the surface tension of TMA or TMLA in aqueous solution is not required.	Not determined.
Water solubility	Trimellitic anhydride (TMA) undergoes practically instantaneous hydrolysis to trimellitic acid (TMLA) on contact with water. It is therefore not possible to determine the aqueous solubility of the parent anhydride and data are provided instead for the hydrolysis product TMLA. The measured aqueous solubility of TMLA is 24.4 g/L at 20°C and pH 1.8 and a similar value of 2.1% (w/w) at 25°C is indicated in published literature. On this basis, TMLA is classed as 'very soluble' in water.	24400 mg/L at 20 °C.
Partition coefficient n-octanol/water (log value)	The octanol/water partition coefficient of trimellitic anhydride (TMA) has been determined experimentally by the HPLC method. The log Kow obtained in this way is 0.06. QSAR modelling performed with the KOWWIN program of the US EPA gives a log Kow estimate of 1.95 for TMA. TMA undergoes almost instantaneous hydrolysis on contact with water, to form trimellitic acid (TMLA). KOWWIN provides a log Kow estimate of 0.95 for TMLA.	Log Kow (Pow): 0.06 at 40 °C.
Flash point	The flashpoint of trimellitic anhydride, determined by a closed-cup procedure, is 227°C.	227°C at 1013 hPa.
Flammability	A preliminary flammability screening test was performed by igniting a loosely-packed linear pile of TMA. The pile failed to ignite during the 2 minutes that a flame was applied to it. According to the UN Recommendations on the Transport of Dangerous Goods, trimellitic anhydride is therefore not classified as a readily combustible solid of Division 4.1 and	Non flammable.

Property	Results	
	further flammability testing is not required.	
Explosive properties	According to theoretical considerations based on chemical structure, trimellitic anhydride does not to possess explosive or oxidising properties. Trimellitic anhydride is unlikely to undergo rapid decomposition accompanied by the evolution of gases or release of heat and therefore does not present a risk of explosion.	Non explosive.
Self-ignition temperature	Trimellitic anhydride (TMA) is a solid at atmospheric pressure. The relative self-ignition temperature of TMA was investigated according to EU Method A.16. No ignition occurred at temperatures up to 400°C, the highest temperature applied (Barbieri, 2010b). The relative self-ignition temperature of TMA therefore exceeds 400°C at atmospheric pressure.	Not applicable.
Oxidising properties	According to theoretical considerations based on chemical structure, trimellitic anhydride does not possess oxidising properties. Trimellitic anhydride is unlikely to cause or contribute to the combustion of other material during transport, storage or use.	Not oxidising.
Granulometry	The particle size distribution of a sample of trimellitic anhydride flakes typical of the Lead Registrant's commercial production was characterised by a sieving method as follows: particles of diameter >100, >500, >1000 and >4000 microns comprised 100%, 100%, 99% and 1.0% by mass, respectively. The data provided by this particle size analysis are compatible with other, independently collated data contributed by members of the Trimellitic Anhydride Sub-Group of the Polyester Monomers Consortium (contributors anonymised, number of sources not known), whose collective particle size distribution data are described by the following envelope: 95% larger than 400 microns, <1% smaller than 50 microns.	95% larger than 400 micron, <1% smaller than 50 micron.
Stability in organic solvents and identity of relevant degradation products	In accordance with REACH Annex IX column 2, this study does not need to be conducted because it is not expected that the stability of trimellitic anhydride in organic solvents is critical.	Not applicable.
Dissociation constant	A waiver is proposed for the parent monomer on the basis that trimellitic anhydride hydrolyses almost instantaneously on contact with water and measurement of its dissociation constant(s) is therefore not technically feasible. Dissociation constants are, however, available for trimellitic acid (TMLA), the hydrolysis product of trimellitic anhydride. At 20°C, the pK1, pK2 and pK3 values of TMLA are 2.91, 3.94 and 5.30, respectively.	At 20°C, the pK1, pK2 and pK3 values of TMLA are 2.91, 3.94 and 5.30, respectively.
Viscosity	In accordance with Section 2 of REACH Annex XI, information requirement section 7.17, this study cannot be conducted on solid materials or gases. According to ECHA Chapter 7 guidance, viscosity measurement is only relevant to liquids.	Not applicable.

2. Harmonised classification and labelling

TMA is covered by Index number 607-097-00-4 in part 3 of Annex VI to the CLP Regulation as follows:

Table 4: Classification according to Annex VI, Table 3.1 (list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008

Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Spec. Conc. Limits, M-factors	Notes
				Hazard Class and Category code(s)	Hazard state-ment code(s)	Pictogram, Signal Word code(s)	Hazard state-ment code(s)	Suppl. Hazard state-ment code(s)		
607-097-00-4	benzene-1,2,4-tricarboxylic acid 1,2-anhydride trimellitic anhydride	209-008-0	552-30-7	STOT SE 3 Eye Dam. 1 Resp. Sens. 1 Skin Sens. 1	H335 H318 H334 H317	GHS08 GHS05 GHS07 Dgr	H335 H318 H334 H317			

H317: Skin Sens. 1 - May cause an allergic skin reaction.
H318: Eye Dam. 1 - Causes serious eye damage.
H334: Resp. Sens. 1 - May cause allergy or asthma symptoms or breathing difficulties if inhaled.
H335: STOT SE 3 - May cause respiratory irritation.

- The following hazard classes are also notified among the aggregated 1042 self-classifications in the C&L Inventory (H332 (28 notifiers) and H370 and H372 instead of H335 (one single notifier) (access date: April 6th 2016).

  H370: STOT SE 1

  H372: STOT RE 1

  H332: Acute Tox. 4

3. Environmental fate properties

Not relevant for the identification of the substance as SVHC in accordance with Article 57 (f) of REACH.

4. Human health hazard assessment

The cyclic acid anhydrides have been reviewed and reported by several organisations, i.e. the OECD SIDS (2002), the Nordic Expert Group (NEG) (Keskinen, 2004), the WHO CICADS (2009) and by the Dutch Health Council (2010). These reports provide an overview of publications including mechanistic toxicology studies, epidemiological studies, case reports etc. With respect to TMA, the substance has been used extensively in toxicology studies where it was used as a typical respiratory sensitiser. TMA has been used to elucidate the mode of action, to develop methods to distinguish between skin and respiratory sensitisers, to study cross-route sensitisation, and to study effects of co-exposure to e.g. irritants. It goes beyond the scope of this Annex XV dossier to cover all these studies. It will focus on those studies showing evidence for (skin or) respiratory sensitisation in humans and on epidemiology and case studies.

4.1 Sensitisation

Toxicological mechanism of TMA sensitisation

Sensitisation is characterised by two phases, i.e. the induction and elicitation phases of sensitisation. These phases are explained as follows:

- During the induction of sensitisation, the immune system develops a heightened susceptibility to react to TMA entering the body. The development of sensitisation may take from days to years of exposure to develop, depending on the intensity, frequency and duration of exposure and the individual. During this time, the immune system is developing an expanded population of T lymphocytes (T-cells) capable of recognising and responding to the chemical. For TMA there is no specific data available on the time required for the development of sensitisation. It is widely accepted that sensitisation arises after a latency period of exposure.

- During the elicitation phase, exposure to TMA evokes the classical type I hypersensitivity inflammatory reaction, resulting for example in chronic inflammation of the lungs. In general, prolonged exposure to respiratory sensitisers can lead to permanent impairment of the lung (Holgate et al. 1999).

The toxicological mechanism of action of TMA, a low molecular weight substance (LMW), is IgE mediated. The IgE mediated pathway basically means the sensitisation process as described above, where specific IgE antibodies play a major role in recognition of the foreign antigen. Maestrelli et al. (2009) state that the presence of specific IgE antibodies may be highly diagnostic and prognostic of occupational asthma.

The location and specificity of the IgE antibody for the epitopes present on the acid anhydride-(hapten)-protein complex have been studied. It has been postulated that the reaction of acid anhydride with albumin alters the albumin to form a new antigenic determinant or that the hapten is altered at the antibody-combining site. There is evidence that in patients sensitised to tetrachlorophthalic anhydride TCPA and TMA, the antibody combines with the anhydride and the adjacent portion of the human serum albumin (HSA) molecule, which is not seen in other cyclic acid anhydrides. TMA forms unique antigenic determinants that do not bind significantly with antibodies formed by sensitisation to phthalic anhydride (PA), hexahydrophthalic anhydride (HHPA) and himic anhydride (HA). This may explain why significant cross-reactivity with TMA has not been found in inhibition studies (Keskinen, 2004 and citations therein; Bernstein et al., 1982; Patterson et al., 1981; Topping et al., 1986; Zeiss et al., 1980; 1982). Furthermore, the TMA-HSA conjugation is very specific for TMA sensitisation.

The anhydride group reacts rapidly with amino acids explaining their conjugation with HSA, which was essentially completed in 1 minute in vitro at 37°C. (Taylor et al., 1987; Zeiss et al., 1977).

Specific IgG antibodies have been studied especially in connection with sensitisation to TMA. Specific IgG antibodies against TMA-HSA have been correlated with late-onset occupational asthma due to TMA. They have also been found in the pulmonary disease-anaemia syndrome due to TMA, as have IgG antibodies to erythrocyte conjugate (Patterson et al., 1978; 1979; 1982; Sale et al., 1981; Turner et al., 1980).

For many LMW substances another pathway leading to similar effects, without specific IgE and perhaps even without triggering the immune system, can occur (Sastre et al. 2003; Maestrelli et al. 2009). Both pathways, the IgE mediated and IgE independent pathways (possibly a cell-mediated immunological reaction), appear to have the same effects on the airways showing airway inflammation, infiltration of inflammatory cells, bronchial constriction and airway remodelling, making it difficult to distinguish between the pathways. A well-known example of a substance that also induces its effects via both pathways is toluene diisocyanate (Sastre et al. 2003) and could theoretically be the case for acid anhydrides as well. Until now, no evidence has been found that indicates that acid anhydrides can or cannot cause occupational asthma through the IgE independent pathway. This IgE independent pathway could explain why certain

symptomatic subjects did not respond positively to the radioallergosorbent test (RAST) against acid anhydrides wherein specific IgE levels are quantified, but still may have an immunological driven reaction. The irritant property of LMW can also lead to asthma like symptoms that will appear rapidly, especially after acute high exposures, often labelled "reactive airways dysfunction syndrome" or "irritant-induced asthma" (Sastre et al. 2003).

4.1.1 Skin

Non-human information

In the aggregated registration dossier two studies on skin sensitisation are summarised (see confidential annex V).

Information from public literature
TMA was included in some sensitisation studies in animals, where TMA's potential to induce allergic contact dermatitis of type IV allergy was investigated, or TMA was used as a topical inducer of a sensitising effect prior to challenge by inhalation. The latter does not provide evidence for skin sensitisation and is reported under respiratory sensitisation. Although, TMA is classified as a skin sensitiser, it seems that the substance is not a potent skin sensitiser and publications by Dearman et al, (1991; 1992; 2000, cited by Keskinen, 2004) seem to indicate that TMA is not a contact allergen in animals at all.

Information from public literature

Moffitt & Sansom (2002) reported a case of a 33-year-old woman with allergic contact dermatitis. Patch tests revealed a positive reaction to phthalic anhydride/trimellitic anhydride/glycols copolymer (1%) ingredient present in nail varnish. This is the only report of consumer exposure to cyclic acid anhydrides.

It is noted that PA seems to be a moderate skin sensitiser in contrast to other cyclic acid anhydrides generally assumed to be low potent skin sensitisers, and thus it cannot be excluded that the symptoms reported by Moffitt and Sansom (2002) were caused solely by PA.

4.2.1 Respiratory system

Non-human information

In the aggregated registration dossier a discussion on the respiratory sensitisation is provided.

Information from public literature:

Many animal studies have evaluated sensitisation effects to characterise the immune response patterns and parameters and elucidate the mode of action of cyclic acid anhydrides. There are also many animal studies conducted with TMA to study the effect of TMA on the lungs and immune system. Sensitisation studies are typically conducted by sensitising animals to a cyclic acid anhydride and challenging the animals with a conjugate of serum albumin and the anhydride. Although there is no validated animal test method available to study or to provide results based upon which a substance can be classified as a respiratory sensitiser, it is widely accepted that effects related to respiratory sensitisation can be picked up in animal studies. Specifically, immune responses have been evaluated after challenge by assessing antibody levels and haemorrhagic lung foci. In summary, the studies describe effects such as obstructive bronchial reactions, bronchoconstriction, bronchospasm, increased airway responsiveness, inflammation of the lungs, haemorrhages, lung lesions, and elevation in anti-body response IgE and IgG, TMA-GPSA or TMA-RSA, and immune cell proliferations. Such effects are indicative of, but not conclusive of, respiratory sensitisation.

A summary table concerning the effects of TMA exposure in test animals from WHO CICADS

(2009) is presented below. It is noted that the table is already out-dated as research to elucidate the mechanism has continued since. The research aimed at finding early detection signals of respiratory sensitisation in animals, which can be used for screening purposes in future in occupational settings, for which TMA is used as a model substance.

Table 5: summary of sensitisation studies in animal studies exposed to TMA (copied from WHO CICADS 2009).

Table 4: Summary of antibody-mediated sensitization studies in animals exposed to cyclic acid anhydrides.

Acid anhydride/ species	Route of administration	Exposure	Effect	Reference
Trimellitic anhydride				
Guinea-pig	Intravenous immunization; inhalation challenge	21–28 days after immunization challenge with 50 µl 1% trimellitic anhydride–guinea-pig serum albumin	Specific IgG_1 and IgE antibodies; increased lung resistance and airway microvascular leakage	Hayes et al. (1992a)
Guinea-pig	Intradermal	0.1 ml of 30% trimellitic anhydride	Specific IgE and IgG antibodies	Botham et al. (1989)
Guinea-pig	Intradermal immunization; intratracheal challenge	Immunization with 0.1 ml of 0.3% trimellitic anhydride; challenge with 50 µl 0.5% trimellitic anhydride–guinea pig serum albumin at 1, 2, 3, 5, or 8 weeks after immunization	Increased lung resistance, extravasation, and specific IgG_1 antibodies, which correlated with extravasation	Arakawa et al. (1993b)
Rat	Inhalation	10–300 µg dust/m^3, 6 h/day for 5 or 10 days	At ≥30 µg/m^3, haemorrhagic lung foci and trimellitic anhydride–rat serum albumin antibodies after 10 days	Zeiss et al. (1987)
Rat	Inhalation	100 µg powder/m^3, 6 h/day, 5 days/week for 2 weeks	Haemorrhagic foci, antibodies in bronchoalveolar lavage fluid, and detection of anti-trimellitic anhydride–rat serum albumin IgG, IgA, and IgM	Chandler et al. (1987)
Rat	Inhalation	330 µg powder/m^3, 6 h/day on days 1, 5, and 10; challenge on day 22 for 6 h with 330 µg powder/m^3	Fewer haemorrhagic lung foci in unchallenged compared with challenged animals; lung injury correlated with antibodies in challenged animals	Zeiss et al. (1989)
Rat	Inhalation	500 µg powder/m^3, 6 h/day on days 1, 5, and 10; challenge on day 29, 6 h to 540 µg/m^3	IgG–, IgM–, and IgA–trimellitic anhydride–rat serum albumin antibodies; haemorrhagic foci, mean 216 per lung	Zeiss et al. (1989)
Rat	Inhalation	500 µg powder/m^3, 6 h/day on days 1 and 5; challenge on day 29, 6 h to 500 µg/m^3	Haemorrhagic foci, mean 112 per lung, good correlation with antibody activity ($P = 0.027$)	Zeiss et al. (1989)
Rat	Intradermal immunization; inhalation challenge	After 3 weeks' challenge with 0.003% or 0.03% trimellitic anhydride–rat serum albumin (15 min) in 1 or 7 days	High levels of specific IgE and IgG; significant rise in bronchial hyperreactivity after repeated challenges; slight damage to airway epithelium in repeat-challenged groups	Cui et al. (1997)
Rat	Inhalation	0.04, 0.4, 4, or 40 mg aerosol/m^3, 10 min, once per week for 10 weeks; challenged with 40 mg/m^3	Specific IgE response, early- and late-phase airway responses, and histopathological changes	Zhang et al. (2006)
Rat	Dermal sensitization; inhalation challenge	Sensitization with 50% w/v and then 25% w/v trimellitic anhydride; inhalation challenge 0.2–250 mg/m^3	Elevated total IgE, laryngeal inflammation, squamous epithelial metaplasia, pulmonary haemorrhages, increase in nonspecific airway responsiveness, decrease in breathing frequency	Arts et al. (2004)
Rat	Intradermal sensitization; inhalation challenge	Sensitization with 1, 5, or 25% trimellitic anhydride applied 2 times at weekly intervals, challenge with 25–30 mg trimellitic anhydride at 17, 24, 41, 47, 55, and 56 days after sensitization	In groups sensitized with ≥5%, altered breathing patterns and increased airway responsiveness	Pauluhn (2003)
Mouse	Inhalation	5000 µg dust/m^3, 1 h/day for 3 days	IgG–trimellitic anhydride–mouse serum albumin antibodies after 1 week, IgE–trimellitic anhydride–mouse serum albumin antibodies after 2 weeks	Dearman et al. (1991)

The following study descriptions were derived from Keskinen (2004), WHO CICADS (2009) and/or the Dutch Health Council (2010) by copying and merging study descriptions from these sources. The studies have been presented per test animal, where after each quote an indication is given in which review(s) the study has been reported by A (Keskinen, 2004); B (WHO CICADS, 2009) and C (Dutch Health Council, 2010):

Rats

[Note: quote of studies starts here]

"Rats pre-treated with the immunosuppressant cyclophosphamide showed no lung lesions and no antibody reaction after exposure to 95 µg/m^3 TMA 6 hours/day, 5 days/week for 2 weeks. Thus, the elimination of T- and B-lymphocyte function could prevent the TMA-induced lesions (Leach et al., 1988). A, B.

The pulmonary disease-anaemia syndrome described due to fumes from TMA cured epoxy resin, is a rare disease with haemorrhagic alveolitis and specific IgG antibodies. In animal studies with rats similar reactions have been found (Chandler et al., 1987; Leach et al., 1987). A, B.

In another study with brown Norway rats both betamethasone and cyclosporin A given over the time of sensitisation inhibited the development of TMA specific IgE and IgG (Pullerits et al., 1997). A

In an inhalation experiment, rats were exposed 3 hours/day for 5 days to 0, 10, 30, 100 or 300 µg/m^3 of TMA dust. Haemorrhagic lung foci were found in relation to exposure concentrations of

30-300 µg/m^3. The serum antibody binding of trimellitic-RSA correlated with exposure concentration, presence of haemorrhagic lung foci and lung weight. The lung lesions had healed 12 days after the exposure, but returned soon after a repeated exposure (Zeiss et al., 1987). A histological examination of the lung lesions indicated extensive cellular infiltration, primarily macrophages, alveolar haemorrhage, and pneumonitis. These effects increased in proportion to the concentration. The lungs were the only organs affected (Leach et al., 1987). A

Chandler et al. exposed rats to TMA powder (100 µg/m^3) for 6 hours/day, 5 days/week for 2 weeks. Haemorrhagic foci were observed on the surface of the lungs at autopsy. The authors found higher total antibody concentrations in the fluid of bronchoalveolar lavage (BAL) than in serum. IgG, IgA, and IgM antibodies to TMA-RSA were detected. Inhibition studies showed that both TMA-RSA and TMA-HSA conjugates cause complete inhibition of the rat IgG binding, whereas the human IgG was inhibited only by TMA-HSA. The early antibody response in the rat was directed towards new antigenic determinants common to TMA-modified albumins. A

The immune response to inhaled TMA has been found to occur in parallel with the development of lung lesions. The antibody levels in BAL and serum were highly correlated with the lung injury (Zeiss et al., 1988). A

After rats had inhaled TMA powder (500 µg/m^3 or 330 µg/m^3) on days 1, 5 and 10 for 6 hours/day they were challenged with TMA (540 µg/m^3 or 300 µg/m^3), on day 29 or 22, respectively. In the high exposure group, IgM and IgA antibodies to TMA-RSA started to increase from day 5 and peaked at day 20. IgG antibodies appeared on day 7 and peaked at day 20. A mean of 216 haemorrhagic lung foci was found. In the low exposure group animals that were not rechallenged had fewer lung foci than the rechallenged animals. In the rechallenged group there was a correlation between all the antibody measures and lung injury. A subgroup of animals was exposed to a TMA level of 500 µg/m^3 only on days 1 and 5 and challenged with 500 µg/m^3, on day 29. A mean of 112 haemorrhagic lung foci was found, and there was a good correlation between the antibody response and the lung injury (Zeiss et al., 1989). A

Brown Norway rats were intradermally sensitised with TMA and then challenged once or seven times with TMA-RSA conjugate. High levels of TMA specific IgE and IgG were found in all the sensitised rats when they were compared with controls. A single allergen challenge did not cause bronchial hyperreactivity but repeated challenge produced significant bronchial hyperreactivity in sensitised rats. Repeated, low-dose challenges produced more hyperreactivity than a 10 times higher single dose. Bronchial eosinophilia was found in the sensitised and single-challenged groups, but not in the non-sensitised non-challenged and sensitised re-challenged groups (Cui et al., 1997). A

When sensitised brown Norway rats were challenged, TMA induced an immediate bronchoconstriction. Eosinophilic aggregates and goblet cell hyperplasia and hypertrophy were seen in the lungs and also induction of haemorrhages in sensitised animals. A less marked eosinophilic infiltration of the lungs was seen also after the challenge tests of the non-sensitised animals (Arts et al., 1998). A

Arts et al. (1997) used brown Norway rats in a very similar setting with TMA, dinitrochlorobenzene, formaldehyde, and methyl salicylate. They also found a significant increase in the serum IgE concentration after exposure to TMA but not after exposure to the other chemicals, skin sensitisers, or irritants. A

Mice

A model to differentiate chemicals for different types of allergenicity has been developed. Mice were sensitised topically, by applying the test material dissolved in 4:1 acetone:olive oil, to a shaved flank under an occluded patch for 48 hours. After 5 days the ear thickness was measured, and then the dorsum of both ears was treated with 25 µl of the tested chemicals, TMA, and 2,4-dinitrochlorobenzene, the latter being a potent contact allergen without respiratory sensitisation properties. When the levels of activation (cell proliferation) in lymph nodes draining the site of

application were similar, comparable levels of contact sensitisation and IgG anti-hapten antibodies were induced by these chemicals, but only TMA increased the IgE production. Furthermore, while TMA induced IgG2b rather than IgG2a antibodies, the reverse pattern was observed with the contact allergen. The results pointed to a different type of T lymphocyte (Th1 and Th2) response to these chemicals (Dearman et al., 1991). A, B.

Guinea pigs

In animal studies using pre-treatment with different blocking agents, the mediators histamine and thromboxane A2 have been shown to be mainly responsible for the early and late bronchoconstriction response to TMA. Leukotrienes and histamine were found to mediate airway plasma exudation to some extent (Arakawa et al., 1993; 1994; Hayes et al., 1992b; 1995). In sensitised guinea pigs, pre-treatment with budesonide significantly inhibited the increase in airway responsiveness, but not the eosinophilic inflammation, induced by exposure to TMA dust (Hayes et al., 1993). A

Activation of inducible nitric oxide synthase has been demonstrated in bronchial tissue after TMA-guinea pig serum albumin (GPSA) challenge in sensitised guinea pigs (Yan et al., 1995). A

Hayes et al. (1992a) developed a guinea pig model for TMA-induced airway hypersensitivity responses by sensitising animals intradermally with 0.1 ml of 0.3% free TMA in corn oil. Control animals were given 0.1 ml corn oil. An increase in the level of specific serum IgG1 antibodies was found in all sensitised animals, and IgE antibodies were detected in 6 of 8 sensitised animals. On days 21 to 28 a tracheal challenge (50 µl) with 1% TMA-GPSA gave increased lung resistance in sensitised animals compared with non-sensitised animals. Airway microvascular leakage was also seen in sensitised animals when tested with Evans blue (Hayes et al., 1992c). When challenged by inhalation through the nose (12 000 µg/m^3 TMA, 30 minutes), the animals showed a significant increase in bronchial reactivity 8 hours after the exposure, and the increase was accompanied by an eosinophilic inflammatory exudate. A

Arakawa et al. (1993) investigated the time course of immune and airway responses after sensitising guinea pigs through two intradermal injections (0.1 ml of 0.3% TMA in corn oil). They challenged the animals after 1, 2, 3, 5 and 8 weeks with 50 µl of 0.5% TMA-GPSA intratracheally. The challenge induced a significant increase in lung resistance, reaching a maximum at 2.5 minutes in the 1-week group and between 5 and 6 minutes in the other sensitised animals. A significant extravasation was also found that increased up to 8 weeks. Specific IgG1 antibodies were detected in all the animals in the 3-, 5-, and 8-week groups; this result correlated with the extravasation but not with the increase in the resistance. A

Inhibiting complement activation prevented inflammatory cell infiltration in TMA-induced asthma. This phenomenon was studied by pre-treatment of guinea pigs with a cobra venom that reduced the complement component C3 in bronchoalveolar lavage fluid after TMA-GPSA challenge. The immediate bronchoconstriction was not affected, nor was the microvascular leakage. The TMA-induced increase in mononuclear cells, total white blood cells and red blood cells, and the erythrocyte peroxidase activity was reduced (Fraser et al., 1995). A

Rhesus monkeys

Dykewicz et al. (1988) sensitised two rhesus monkeys intrabronchially with serum from a worker with TMA asthma and high titres of IgE, IgG, and IgA to TMA-HSA. The monkeys were challenged with TMA-HSA aerosol and bronchospasm appeared. After 1 week the challenge was negative. Passive cutaneous anaphylaxis was also found with the Prausnitz-Küstner test." A

[End of quote]

Human information

The CSR refers to the CICADS document from the WHO (2009), which is included integrally in the registration dossier, but does not include any further human information.

Information from public literature

To date, respiratory sensitisers have only been classified based on human evidence. In the public literature there are industrial surveys, case studies and epidemiological studies reported. Keskinen (2004), WHO CICADS (2009) and the Dutch Health Council (2010) previously reported the studies described below. The cases described were all reported before 2000, no recent cases have been reported to our knowledge.

Keskinen (2004) made an overview of studies where workers were occupationally exposed to TMA, amongst other cyclic acid anhydrides. The table is copied in below (Keskinen, 2004).

Table 6: effects of TMA in occupationally exposed subjects (copied from Keskinen, 2004).

Table 11. Effects of cyclic acid anhydrides in occupationally exposed.

Anhydride/ Exposure level ($\mu g/m^3$)	No of exposed	Exposure duration m=months, yr=years	Symptoms, effects	Specific IgE	Specific IgG	Skin prick tests	Reference
TMA							
1 700-3 600 (TWA)	9	m-10 yr	Irritation 4/9 Asthma 3/9	1/9	4/9		(109)
10-2 100	18	8.6 yr	Rhinitis 1/18 Asthma 3/18	1/18, total TMA-HSA antibodies 4/18			(20)
TMA							
<1-100	11	2 yr	No symptoms	No antibody response			(124)
		Not given					(213)
170 (GM)	8		Asthma/rhinitis 2/8	25%			
87	39			0%			
<0.55	98		Asthma 1/98	0%			
<0.41	123			0%			
<0.53	42			0%			
full-shift		>1 m				TMA-HSA:	(13)
<10	63					1/63 (OR 1.00)	
10-40	36					5/36 (OR 10.00)	
>40	8					2/8 (OR 20.67)	
full-shift		>1 m	Risk of new work-related respiratory symptoms:				(13)
<10	44		5/44 (OR 1.00)				
10-40	13		6/13 (OR 5.94)				
>40	3		1/ 2 (OR 7.42)				

References in the table are:
13: Barker et al. 1998
20: Bernstein et al. 1983
109: Letz et al. 1987
124: McGrath et al. 1984
213: Zeiss et al. 1992

Epidemiological studies

The table below is copied from the Dutch Health Council (2010) describing two epidemiological studies (follow-up study and a cross-sectional study) in workers:

Table 7: human data on TMA induced IgE-mediated sensitisation (copied from Dutch Health Council, 2010).

Table 3.1 Human data on TMA-induced IgE-mediated sensitisation.

Study design	Exposure category	TMA-specific IgE-mediated sensitisation (elevated IgE antibody)
Grammer *et al.* (1999).[15] Three-year clinical and immunologic survey, USA; TMA manufacturing facility; 286 employees. None of the employees had been diagnosed as having an immunological mediated disease by TMA.	Mean (range) in µg/m³ 1: 130 (31,700) 2: 36 (2.3-1,900) 3: 2 (0.1-120) 4: 0.5 (0.2-2.4) 5: <0.5 (<0.5-<0.6)	No. of positive employees: 1: 7/28 (=25%) 2: 6/57 (=11%) 3: 5/79 (= 6%) 4: 0/98 (= 0%) 5: 0/24 (= 0%) Relationship (weak but positive) between IgE antibody and exposure class (p<0.0002 ; effect strength = 28.2 (values less than 40 are considered relatively weak)).
Zeiss *et al.* (1992).[37] One-year cross-sectional survey, USA; TMA manufacturing factory; 321 new enrollees; period 1988-1989.	Geometric mean (range) in µg/m³: 1: 170 (<0.5-6,500) 2: 87 (5.8-970) 3: <0.55 (-) 4: <0.41 (<0.3-<0.6) 5: <0.53\ (<0.5-<0.6)	No. of positive cases after one year of exposure: 1: 2/8 (=25%) 2: 0/39 (= 0%) 3: 0/98 (= 0%) 4: 0/123 (= 0%) 5: 0/42 (= 0%)

The following study descriptions were derived from Keskinen (2004), WHO CICADS (2009) and/or the Dutch Health Council (2010) by copying and merging study descriptions from these sources. The studies have been presented, where after each quote an indication is given in which review(s) the study has been reported by A (Keskinen, 2004); B (WHO CICADS, 2009) and C (Dutch Health Council, 2010):

[Note: quote of studies starts here]

"In a study by Grammer et al. (1999), 286 workers were annually investigated for the appearance of TMA-induced allergic respiratory disease, for three consecutive years. The workers were assigned to five exposure classes by type of job; exposure levels of the classes were based on some industrial hygiene measurements (personal monitoring). None of the 24 workers in the lowest exposure class (class 5; mean <0.5 µg TMA/m^3) developed allergic sensitisation or respiratory symptoms during the observation period. Of the 98 workers in class 4 (mean 0.5 µg TMA/m^3) nine were positive for the presence of specific IgG. No other effects were observed. In the three highest classes with mean exposure of 2 to up to 130 µg TMA/m^3, part of the workers had specific IgG or IgE against conjugates of TMA in their blood, and part of them also reported respiratory symptoms. The authors reported that the strongest exposure-response-related effect was the increase of percentage of workers positive for specific IgE. Based on their findings the authors suggested furthermore that workers exposed to less than 2 µg TMA/m^3 are at low risk of developing TMA-induced allergic respiratory disorders. Later, the same authors reported on disease status of 42 workers who developed allergic lung disorders and were transferred to low-exposure jobs (Grammer et al., 2000). In 35 individuals, symptoms disappeared, pulmonary functions improved, and specific IgG and IgE levels decreased. In a separate study, 25 workers with occupational asthma were questioned about disease development (Grammer et al., 2002). Most of them reported also symptoms associated with rhinitis and conjunctivitis. They also reported that these symptoms preceded asthma symptoms. B, C.

Zeiss et al. (1990) conducted a 12-year (1976–1987) clinical and immunological study of 196 workers in the trimellitic anhydride manufacturing industry. The workers were administered a questionnaire and tests for total trimellitic anhydride antibodies and trimellitic anhydride–specific IgE. IgE-mediated immediate-type asthma or rhinitis was found in 21 workers and late-type asthma in 10 workers. A total of 113 workers had only irritant symptoms, and 46 were asymptomatic. A low level of total antibodies was found for TMA-HSA in 16% and 8%,

respectively.No data were available on exposure, but there was an annual decline in the number of sensitized workers due to improvements in the workplace. A

In the same factory, in a cross-sectional study by Zeiss et al. (1992), of 474 workers in 1988-1989 with a very similar setting, five exposure groups were assigned by an industrial hygienist on the basis of job history and the results of personal monitoring of some employees in each exposure class. The group mainly consisted of new enrolees (n=321). Seven per cent had an immunological syndrome due to TMA exposure, and 32% had irritant symptoms with low specific total and IgE antibody levels. Sixty-two per cent had no work-related symptoms and very few or no antibodies. The mean total antibody levels and mean IgE antibody levels decreased according to the exposure level. TMA specific IgE antibodies were found only in the high exposure group (0.54-6 500 µg/m^3, geometric mean 170 µg/m^3) whereas the findings were negative in four other groups with exposure less than 6-970 µg/m^3 (geometric mean 87 µg/m^3) of TMA. The sensitisations and illnesses due to TMA were concentrated into the three upper exposure groups, and therefore efforts to reduce exposure were suggested. A group of new employees not evaluated earlier for an occupational disease were analysed for total TMA-HSA antibody levels by age, sex, date of hire and smoking. Only current or former smoking was associated with the total antibody levels (chi-square=6.45, p=0.01). Atopic status was not assessed. One year after 29 sensitised workers had been moved to low-exposure jobs, their symptoms and pulmonary functions had improved and the specific antibody levels had decreased (Grammer et al., 1993). A, C.

No TMA–related disease was found over a 2-year period among 11 factory workers preparing epoxy resin coating material. The TMA exposure level was less than 180 µg/m^3 (McGrath et al., 1984). The study population was small; therefore it is difficult to make a final conclusion on these findings. A.

Altogether 119 TMA-exposed workers were followed for five years to determine whether they would develop a respiratory disease. Sixteen had TMA specific IgE antibodies and 3 of them had asthma in the beginning. Another 6 developed asthma during the 5-year follow-up period. One of the 102 workers with no specific IgE antibodies developed asthma. Specific IgG antibodies were detected in 44 subjects, 6 had a non-immediate respiratory disease in the beginning and 2 more were found after five years. None of the IgG-negative workers developed a respiratory disease (Grammer et al., 1998). In a study of 57 HHPA-exposed workers, 7 had IgE and IgG-mediated respiratory disease whereas 9 had only IgE-mediated disease. An association was found between the development of respiratory disease and specific IgE and IgG antibodies, as well as an association with the level of exposure but not with smoking (Grammer et al., 1994). Skin prick test reactivity to common allergens in 33 employees with respiratory symptoms due to HHPA showed that atopy had only a marginal clinical significance as a risk factor for disease (Grammer et al., 1996). A, B.

In a case-control study of 16 persons with TMA asthma and 44 similarly exposed controls, determinations of specific IgE against four common environmental allergens were carried out. Fifty-six per cent of the cases and only 29% of the controls were found to be atopic (Sikora et al., 1999). A.

Risk factors for sensitisation and respiratory symptoms were evaluated in a historical cohort study consisting of 506 workers from four factories. The cohort was defined as all workers with exposure to anhydrides for more than one month since the beginning in 1960. Three factories manufacturing resins used principally PA, but also MA and TMA were used. One factory produced cushioned flooring and used only TMA. The exposure was assessed retrospectively, by job. The current full-shift and task-specific exposure measurements, the past exposure data and qualitative information were used and exposure estimates were calculated in the job-time-exposure matrices (Van Tongeren, 1998). The questionnaire, comprising employment history, respiratory symptoms and smoking habits, was completed by 401 workers (79%). Skin prick tests with common inhalant allergens and anhydride conjugates were carried out. Thirty-four persons (8.8%) had respiratory symptoms related to anhydride exposure, and 12 (3.2%) were

sensitised according to the skin prick tests with anhydride conjugates. Sensitisation was associated with work-related respiratory symptoms and with smoking, at the time of the exposure to acid anhydride. An exposure-response relationship was not found overall, but in the factory with exposure to TMA an increased prevalence of sensitisation and work related symptoms with increasing full-shift exposure. Barker et al. (1998) examined 63 workers exposed to trimellitic anhydride. The prevalence of sensitization and work-related symptoms increased with increasing exposure. The odds ratios for positive skin prick tests for workers exposed to 10–40 μg/m^3 and >40 μg/m^3 compared with workers exposed to <10 μg/m3 were 10.0 and 20.7, respectively. The odds ratios of work-related respiratory symptoms in those exposed to 10–40 μg/m^3 and >40 μg/m^3 were 5.9 and 7.4, respectively. There was no increase in prevalence of sensitization or symptoms with smoking or atopy. A, B, C.

The association of human leukocyte antigen (HLA) allele frequency and specific IgE antibody to acid anhydride-HSA conjugates has been investigated to determine a possible genetic influence on sensitisation. Thirty workers with work related respiratory symptoms with specific IgE antibodies had been exposed to PA, TMA, or TCPA. Thirty referents were exposed to PA or TMA. A similar proportion of both the cases and referents were atopic and smokers, the other risk factors for this sensitisation. A significant excess of HLA-DR3 loci were found in cases with specific IgE to acid anhydrides when compared with the controls (50% versus 14%). A relationship was found between HLA-DR3 and specific IgE antibodies for TMA and possibly for TCPA but not for PA. The difference in the epitope was suggested as the reason for the different findings (Young et al., 1995). A.

Blomqvist et al. (2005) studied the prevalence of respiratory symptoms and immunological responses among 119 powder painters, working in six different shops. They also described exposure levels of TMA. In these paints, resins are used as binding agent, and for the manufacturing of these resins cyclic acid anhydrides are used. Part of the acids may remain in the paint. Data on exposure was limited to one shop. In that shop personal exposure measurements revealed airborne concentrations of between 6 and 180 μg TMA/m^3, and stationary samples had concentrations between 15 and 1,040 μg TMA/m^3. In a spray booth the exposure was 200 μg TMA/m^3, whereas outside the spray booth it was less than 3 μg TMA/m^3. Medical examination and lung function testing revealed work related symptoms, such as eye irritation, nasal discharge, blockage and nose bleeding, sneezing, sore and dry throat, cough and asthma symptoms. In some of these workers also specific IgG in the blood could be detected, but in none of the workers specific IgE was found. Overall, the authors stated that the study population may have been not representative of powder sprayers in general. They also suggested that respiratory irritation may have been caused by the dust of the powder, rather than TMA itself. C.

Clinical case reports and surveys

In industrial surveys, the prevalence of occupational asthma due to different anhydrides has varied between 2-11% for TMA exposure (Yokota et al., 1999). According to the Finnish Register of Occupational Diseases, cyclic acid anhydrides caused the following numbers of diseases relative to the total numbers in 1997-1999: asthma 1/902, rhinitis 14/1 001 and contact urticaria 8/478. There were no reports of allergic alveolitis or allergic contact
dermatitis (Karjalainen et al., 1998; 1999; 2001). A, C.

In TMA-exposed workers, the levels of IgG1-4 subclasses against TMA-HSA did not differ between workers with and without a TMA-induced immunological lung disease (Gerhardsson et al., 1992). A.

Both immediate- and late-type respiratory allergies have been reported due to TMA. Both begin after a latency period. Specific IgE antibodies have been found in immediate-type rhinitis and asthma (Patterson et al., 1982; Zeiss et al., 1977). In the late-type respiratory syndrome the worker experiences coughing, wheezing and dyspnoea, starting 4-8 hours after the exposure. The respiratory symptoms have been accompanied by malaise, chills, fever, myalgia and

arthralgia. No specific IgE antibodies are found, but IgG and IgA antibodies are present. The disease has not been verified with challenge tests. A.

Pulmonary disease-anaemia syndrome due to TMA is a disease first reported by Rice et al. in 1977. Herbert and Orford (1979) reported seven more cases in 1979, and Ahmad et al. (1979) presented another two in 1979. All cases had been exposed to fumes from TMA-cured epoxy resin sprayed on hot pipes. The symptoms were cough, haemoptysis, dyspnoea, pulmonary infiltrates, restrictive respiratory defect, hypoxaemia, and anaemia. The symptoms ranged from mild to very severe. IgG antibodies have been found to both human serum conjugate and erythrocyte conjugate of TMA. Open lung biopsy has shown intact alveolar septae and extensive intra-alveolar haemorrhage with granular pneumocyte hyperplasia. Immunofluorescent studies were negative, suggesting that the antibodies were not involved in the tissue injury. Patterson et al. (1982) did not find any IgE antibody activity against trimellityl-HSA (TM-HSA) in workers with pulmonary disease-anaemia syndrome. IgG activity against TM-HSA did not differ from the level in other workers exposed to TMA fumes under similar work conditions. IgG, IgA and IgM antibodies were found against TMA-human erythrocytes (Patterson et al., 1979). Later, antibodies to TMA-human erythrocytes were also found in workers with asthma due to TMA, but not in unexposed persons (Turner et al., 1980). A.

Letz et al. (1987) examined all nine workers at a barrel manufacturing plant who were exposed to TMA breathing zone concentrations of 1700–3600 µg/m^3. Four workers had trimellitic anhydride–induced irritant effects. Three had symptoms and IgG levels consistent with late-type respiratory syndrome, one had specific IgE against trimellitic anhydride, and one worker was asymptomatic. One worker had bronchitis not related to TMA. A, B.

One case of allergic alveolitis has been reported in connection with exposure to both TMA and PA. The worker was exposed to the dust and fumes of polyester powder paint during a malfunction of the ventilation of the factory hall. The paint contained small amounts (<1%) of both TMA and PA. The diagnosis was based on the follow-up of the symptoms and on the findings in chest radiographs and BAL, as well as on the presence of fever and a slight reduction in the transfer factor after a short re-exposure at work (Piirila et al., 1997)." A.

[End of quote]

The UK MSCA indicated that: "The Health and Occupation Research Network (THOR) collects and disseminates data on work related ill-health for the UK and there have been no cases of occupational asthma linked to TMA reported between 2005 and 2014 (chest physicians and occupational physicians) and between 2006 and 2015 (general practitioners)."

Potency of TMA in relation to other cyclic acid anhydrides

Other cyclic acid anhydrides have been recognised as potent respiratory sensitisers. From the limited epidemiological data available on cyclic acid anhydrides, it appears there is a difference in potency. TMA is among the more potent cyclic acid anhydrides, often used for this reason as a model substance in animal studies as positive control or to study the mechanism of respiratory sensitisation. For two cyclic acid anhydrides (HHPA and TMA) sufficient epidemiological data was available to calculated reference values according to The Health Council of the Netherlands. The reference values corresponding to an additional risk of sensitisation of 10% are 0.73 µg/m^3 and 18 µg/m^3 for HHPA and TMA respectively.

In the table below (copied from Keskinen (2004)), the exposure levels at which the critical effects are expected based on human data are given.

Table 8: critical effect levels in man for cyclic acid anhydrides (copied from Keskinen, 2004).

Table 12. Critical effects (sensitisation and work-related symptoms) in man with corresponding exposure levels of cyclic acid anhydrides.

Acid anhydride	Exposure level ($\mu g/m^3$)	Critical effect	Reference
PA	1 500 –17 400	Sensitisation Asthma	(136)
TCPA	140-590	Sensitisation Work-related respiratory symptoms	(118)
TMA	10-40	Sensitisation Work-related respiratory symptoms	(13)
HHPA and MHHPA	10-50	Sensitisation	(195)
MTHPA	5-20	Sensitisation Rhinoconjunctivitis Asthma	(134, 202)

Reference 13 for TMA: Barker et al., 1998.

4.3.1 Summary and discussion of sensitisation

Based on the information in the CSR the registrants have concluded that (which is in line with the harmonised classification):

"*Skin Sensitisation*

The substance is considered to be a skin sensitiser based on the results of a positive Buehler study. It is classified as a skin sensitiser with the symbol Xi and the risk phrase R43 " May cause sensitisation by skin contact" according to Directive 67/548/EEC. It is classified as skin sensitiser Category 1 and assigned the hazard statement H317 "May cause an allergic skin reaction" according to Regulation (EC) No 1272/2008.

Respiratory Sensitisation

TMA is classified as a respiratory sensitiser with the symbol Xi and is assigned the risk-phrase R42 " May cause sensitisation by inhalation" according to Directive 67/548/EEC. It is also classified as Category 1 for respiratory sensitisation with the symbol "Danger" and is assigned the hazard statement H334 "May cause allergy or asthma symptoms or breathing difficulties if inhaled".

In summary, the epidemiological studies and case studies between 1990 and 2006 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 ug/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 some studies indicated that most workers showed symptoms, without specifying a number. Those workers were not represented by the figures above. Furthermore, only the data specifically related to TMA alone are summed up, thus not including summary reports of cyclic acid anhydrides. In the UK no occupational asthma cases related to TMA have been reported in the period between 2005 and 2015.

Conclusion

It is beyond doubt that the substance is a respiratory sensitiser based on findings in animals and

humans. Moreover, TMA has a harmonised classification for respiratory sensitisation. Animal data indicated a lowest reported LOAEL of 2 µg/m^3 in the rat. Human data indicate that effects may already occur at 10 µg/m^3, where the Dutch Health Council established additional risk levels (at 0.1% and 1%) of 0.18 and 1.8 µg/m^3.

With respect to the potency to induce or elicit respiratory effects in humans TMA is a rather potent respiratory sensitiser. Compared to other cyclic acid anhydrides its potency is in the same range as that of hexahydrophthalic anhydride (HHPA), hexahydromethylphthalic anhydride (MHPPA) and slightly less potent than methyltetrahydrophthalic anhydride (MTHPA), though the ranges still overlap (Keskinen, 2004). The Dutch Health Council derived risk levels for TMA and HHPA showing a much larger difference in potency, i.e. 0.73 µg/m^3 and 18 µg/m^3 for HHPA and TMA, respectively for the 10% additional risk levels. The differences between the Dutch Health Council and Keskinen can be ascribed to the use of the critical study by Rosqvist et al., (2003, as cited by Health Council of the Netherlands, 2010) for HHPA that was not available to Keskinen (2004), and the fact that the data for HHPA showed a more steep relationship resulting in a relatively low benchmark dose for the lower confidence limit (BMDL).

5 Environmental hazard assessment

Not relevant for the identification of the substance as SVHC in accordance with Article 57 of (f) REACH.

6 Conclusions on the SVHC Properties

6.1 CMR assessment

Not relevant for the identification of the substance as SVHC in accordance with Article 57 (f) of REACH.

6.2 PBT and vPvB assessment

Not relevant for the identification of the substance as SVHC in accordance with Article 57 (f) of REACH.

6.3 Equivalent level of concern assessment

6.3.1 Summary of the data provided

TMA has a harmonised classification for respiratory sensitisation according to Annex VI, Table 3.1 (list of harmonised classification and labelling of hazardous substances) of Regulation (EC) No 1272/2008 (index number: 607-097-00-4). The classification of respiratory sensitisation is based on human evidence including case reports and cross-sectional studies on respiratory sensitisation in occupational settings (Keskinen, 2004; WHO, 2009; Dutch Health Council, 2010). Supportive evidence is obtained in inhalation studies in the rat showing immunological responses in the lungs.

The guidance on the identification of SVHCs indicates a number of factors that should be taken into account when considering whether a substance shows an equivalent level of concern to CMR (cat 1 or 2) substances; seriousness of effects, irreversibility of health effects, the consequences for society, and difficulty in performing concentration-based risk assessment are mentioned to be important. They are discussed in the sections below. Details on the sensitising properties of TMA are provided in chapter 4.

6.3.2 Equivalent level of concern assessment

The seriousness of the effect

The chemical properties of certain substances can possibly lead to health effects, in a proportion of individuals who have been exposed to these substances. The extent of these health effects can range from mild to serious[5], depending on e.g. the properties of the chemical, the extent of the exposure (concentration and duration) and a number of other factors.

Exposure to substances classified as carcinogenic or mutagenic has the potential to cause serious health effects in a proportion of the population i.e. serious and permanent organ dysfunction, inheritable defects and/or death.

Exposure to substances classified as toxic to developmental reproduction also has the potential to cause serious health effects in a proportion of the population i.e. serious and permanent organ dysfunction, defects and/or death.

In the case of TMA, a respiratory sensitiser, serious and permanent organ dysfunction is a possible outcome. TMA is known to sensitise subjects at the workplace and is known to cause occupational asthma, rhinitis/conjunctivitis, and pulmonary disease-anaemia syndrome in a part of exposed individuals (WHO 2009). The effects of occupational asthma are severe and may include permanent impairment of lung function if subjects continue to work under exposure. The underlying mechanism (regardless of type of sensitisation (Sastre et al. 2003)) is described by Holgate et al. (1999) and represented in a simplified manner as follows: prolonged inflammatory reactions in the lungs result in lung epithelia that are continuously under stress and will be held in the repair 'mode'. The epithelial injury, pro-inflammatory products and repair or growth factors that are constantly present can drive airway 'wall' remodelling to protect the lungs from further injury. A key issue is that there might be irreversible damage to lung functions, before it is appreciated that there is a health problem. While health effects such as coughing may be mild at first, if exposure is prolonged at the workplace the health effects can become more serious leading to occupational asthma and permanent lung impairment eventually. Permanent lung impairment is not regularly seen in occupational disease registries, because occupational asthma often already inhibits working and is considered to be incapacitating, and is difficult to establish. In addition, exposure to the allergen can cause asthma attacks and thus both chronic and acute severe effects may result from exposure. Acute high exposures may lead to the reactive airways dysfunction syndrome.

The case reports and epidemiology studies in worker populations (in Chapter 4) 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 ug/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 likely underestimates. Some of the effects have been so severe that subjects were forced to leave their job. It is noted that most cases are reported for the period 1990-2006, more recent cases have not been found in the literature.

[5] In the context of the '*Guideline on the definition of a potential serious risk to public health in the context of Article 29(1) and (2) of Directive 2001/83/EC'* the term 'serious' means a hazard that could result in death, could be life-threatening, could result in patient hospitalisation or prolongation of existing hospitalisation, could result in persistent or significant disability or incapacity, or could be a congenital anomaly/birth defect or permanent or prolonged signs in exposed humans.

Irreversibility of health effects

An irreversible health effect is a permanent change in the structure and/or function of an organ system or a permanently increased risk of suffering from a disease or some other threat to health. Irreversible effects can vary in intensity and are related both to: the amount and duration of exposure and the age at which the person is initially exposed. A risk or effect may diminish over time, but it may also increase; some risk may remain many years after exposure has ended (Brodish 1998; on permanent lung damage after cigarette smoking).

Exposure to substances classified as carcinogenic or mutagenic could lead to cancer which can lead to death or irreversible morbidity in a proportion of the population.

Exposure to substances classified as toxic to developmental reproduction has the potential to cause irreversible malformations, abnormalities and irreversible morbidity.

Exposure to TMA has the potential to induce irreversible sensitisation to the substance. Sensitisation in itself is irreversible but not an adverse effect *per se*. It is only when the sensitised individual is exposed to TMA again, that signs of e.g. asthma, rhinitis and/or conjunctivitis will occur. The IgE antibodies, needed for recognition in the hypersensitivity process, remain in the human body for a very long time and are formed as long as the subjects are exposed. The half-life of IgE immunoglobins can vary from several months to years (Sastre et al. 2003) and in most cases will practically mean that a subject is sensitised for the rest of their life. As previously described, prolonged exposure can lead to permanent lung damage as lung walls are remodelled if the lungs are under continuous stress. This results in asthma-like symptoms (e.g. shortness of breath) that will remain even without TMA exposure.

Delay of health effects

As mentioned in the previous sections 4.1 sensitisation and section 6.3.2 on the seriousness and irreversibility of the effects:

Sensitisation is characterised by two phases, i.e. the induction and elicitation phases of sensitisation. These phases are explained as follows:

- During the induction of sensitisation, the immune system develops a heightened susceptibility to react to TMA entering the body. The development of sensitisation may take from days to years of exposure to develop, depending on the intensity, frequency and duration of exposure and the individual. During this time, the immune system is developing an expanded population of T lymphocytes (T-cells) capable of recognising and responding to the chemical. For TMA there is no specific data available on the time required for the development of sensitisation. It is widely accepted that sensitisation arises after a latency period of exposure.

- During the elicitation phase, exposure to TMA evokes the classical type I hypersensitivity inflammatory reaction, resulting for example in chronic inflammation of the lungs. In general, prolonged exposure to respiratory sensitisers can lead to permanent impairment of the lung (Holgate et al. 1999).

The underlying mechanism (regardless of type of sensitisation (Sastre et al. 2003)) is described by Holgate et al. (1999) and represented in a simplified manner as follows: prolonged inflammatory reactions in the lungs result in lung epithelia that are continuously under stress and will be held in the repair 'mode'. The epithelial injury, pro-inflammatory products and repair or growth factors that are constantly present can drive airway 'wall' remodelling to protect the lungs from further injury. A key issue is that there might be irreversible damage to lung functions, before it is appreciated that there is a health problem. While health effects such as coughing may be mild at first, if exposure is prolonged at the workplace the health effects can become more serious leading to occupational asthma and permanent lung impairment eventually.

Therefore, it may be concluded that there is a delay in sensitisation effects and if ill-considered or not sufficiently recognised may progress to more serious effects.

Other factors

Quality of life

A person's quality of life can be compromised as a direct result of the adverse health effects potentially brought on by exposure to carcinogens and mutagens. Possible side-effects such as organ dysfunction can result in the person having to live with a long term illness, limiting the possibility of living a normal working and private life.

The prognosis of a person with cancer could range between 0 and 100% chance of survival. A person with cancer having a very high change of survival may go into remission (and may live a full and 'normal' life), however there is always a chance that the cancer could return. Regardless of the prognosis, the effect caused by exposure to carcinogenic chemicals resulting in cancer is considered as a serious consequence in general, as it always has the potential of being fatal.

In the case of developmental toxicants, depending on the effect manifested, the long-term consequences for the infants/person may be very severe and impair the quality of life. Children having developmental effects may need life-long medication and/or support during their daily life. There is also an indirect effect on the quality of life of such children's parents in terms of emotional investment, care and financial resources needed.

A sensitised person may still be able to lead a relatively 'normal' life away from the workplace however this consequence of exposure could still be categorised as a 'serious effect', when the changes to his/her quality of life is considered. In the case of TMA, permanent impairment of lung function due to TMA induced occupational asthma, as a worst case example, can lead to a decreased quality of life and a requirement for long-term medication. In most cases, the need to eliminate exposure means that the person cannot work in their chosen profession any longer. Re-training of affected individuals in the workplace can also impair that person's quality of life.

The consequences for society

There is a certain level of concern in society when it comes to chemicals, especially in terms of where they end up and what type of effect they can have on a person's health.

In general, there is widespread concern in society regarding cancer (carcinogens/mutagens), due to the uncertainty of the future effects, which may arise e.g. development of cancer and potential death.

The potential adverse effects on children (developmental reprotoxicity) e.g. severe malformations or restrained intellectual capabilities causing a limited quality of life are of high concern for the society. There can also be a high cost of treating affected individuals in society.

Health effects caused by TMA after prolonged exposure can lead to permanent disability as the lungs are 'restructured', which can be viewed as a concern within society, but occupational asthma is already considered one of the most important occupational diseases. Besides health effects, there can also be a significant cost of treating affected individuals in society. Furthermore, when respiratory sensitisation is caused by the working conditions, workers are not able to perform their original work anymore and have to be assigned other work or will need to be re-trained to perform other work. Once occupational asthma has developed, the restrictions in work may go beyond those workplaces where TMA is used, but can have consequences for other workplaces, for example dusty environments. Costs to society can be high, if absenteeism, loss of jobs, and medical treatments are considered.

There are some estimates for cyclic acid anhydrides as a group in the Netherlands. It is estimated by the Health Council of the Netherlands that at least a thousand people in the Netherlands are occupationally exposed to acid anhydrides (Health Council of the Netherlands 2008). In their

report, it is stated that:

"*Figures for the prevalence of work-related sensitisation to anhydride conjugates vary from about 13 to 38% (for specific serum IgE and/or IgG) and from about 8 to 17% (for SPT with serum albumin anhydride conjugates). No specific sensitisation to these agents was detected in unexposed people. Greater exposure and atopy were found to increase the likelihood of specific IgE-mediated and/or IgG-mediated sensitisation. Among people occupationally exposed to acid anhydrides, the prevalence of occupational asthma was up to 30%. Similar prevalences of nasal disorders have been reported. For nasal disorders, a corresponding figure of 30 to 49% has been reported, and a figure of 62 to 85% for nasal haemorrhage. There is considerable spread in the prevalences quoted for acid anhydrides. This is attributable partly to differences in exposure level, in the type of anhydride and in the nature of the industrial use*."

Difficulty in performing concentration-based risk assessment

For most substances a hazard and risk assessment can be performed. In such assessments a no effect "safe" level can be determined from human or animal data providing a DNEL (Derived No-Effect Level). These levels can be compared to the predicted exposure levels to determine the risk. For some hazard classes the available information may not enable a toxicological threshold and therefore a DNEL to be established.

For mutagenic carcinogens, it is only possible to conclude 'zero risk' if there is no exposure. In certain cases, even very small doses of carcinogenic substances can cause adverse effects, which may only manifest after several years of exposure. Consequently, derivation of a safe level is not possible. Under REACH a DMEL will be derived for such substances.

For substances causing developmental effects it is normally possible to determine a toxicological threshold and consequently a safe concentration.

In the case of respiratory sensitisers, it is difficult to establish what the threshold dose is for the induction and elicitation phases of response. Firstly, there are currently no accepted or validated animal tests available to test for respiratory sensitisation for classification purposes, nor do the studies conclusively determine a respiratory sensitising effect. Hence, it is not possible to derive a dose-response relationship. Therefore, the identification of respiratory sensitisers relies on human data, mainly from epidemiological studies or case reports. The data in those studies often lack sufficiently detailed exposure information to derive a no effect level. The toxicological endpoint further makes the risk assessment difficult. The sensitising (induction) dose may vary significantly between individuals. Although it is plausible that a threshold exists below which no allergic sensitisation may be expected, in most cases the threshold level will be too low to discern using the techniques presently available.

It is commonly believed that the elicitation threshold lies even lower than the sensitisation threshold and may not even be identified due to technical restrictions (e.g. response already occurs at or below level of detection). Consequently, the derivation of a safe concentration is not routinely possible and any figure derived would be associated with large uncertainty. This in turn leads to difficulties in assessing whether the risk management measures in place (or envisaged) are suitable to control the risk to an adequate level. Instead, in some cases a reference value, a concentration level that corresponds to a predefined accepted level of risk of allergic sensitisation, can be calculated when appropriate human data are available, e.g. a DMEL could be derived. It should however be noted that protection of naive subjects of becoming sensitised, does not necessarily also protect the already sensitised subjects.

Recently, the Health Council of the Netherlands has proposed a method to derive reference values for respiratory sensitisers based on sensitisation as critical effect since it plays a crucial biological role and is a prerequisite for the development of allergy. Although it is plausible that a threshold exists below which no allergic sensitisation may be expected, in most cases the threshold level will be too low to discern using the techniques presently available. Instead, a reference value is calculated, a concentration level that corresponds to a predefined accepted level of risk of allergic sensitisation (Health Council of the Netherlands 2008; 2010).

The Dutch Health Council (2010) on the derivation of additional risk levels for non-sensitised subjects:

"*Two epidemiological studies on the relationship between exposure to TMA and the occurrence of allergic sensitisation and respiratory symptoms have been reported. These are the studies by Grammer et al. (1999), and by Zeiss et al. (1992), both of the same research group, but with different study populations.*

First, the committee emphasises that the observation period in both studies was rather short. Since it is known that new cases of allergic sensitisation can occur, even after years of occupational exposure, it is most likely that new cases would have been reported when the observation period had been longer. Furthermore, it should be taken into account that variations in exposure levels have occurred during work, although its significance on quantitative risk analysis cannot be assessed. In addition, workers were assigned in an exposure class by type of job; exposure levels of the classes were based on some industrial hygiene measurements (personal monitoring). These factors may have weakened the strength of the exposure and response data.

Regarding the study of choice, according to Dutch Expert Committee on Occupational Standards (DECOS), quantitative risk assessment is best done by using data of the Grammer-study, because of the cohort design. In epidemiology, in controlling selection bias, cohort designs are preferred above cross- sectional designs. Furthermore, the Grammer-study had a more extended set of data on adverse health effects, other than IgE-mediated sensitisation, than the Zeiss-study.

Subsequently, the committee used the curving fitting program of the Bench Mark software of the US-EPA for the fitting the data of the Grammer study. In Annex E, details and the outcome of the curve fitting analyses are shown. Regarding the data, no cases were reported by Grammer et al. (1999) of IgE mediated allergic sensitization in a group of workers exposed to 0.5 mg/m^3 and lower. This might indicate the presence *of a safe threshold level. However, the committee doubts whether from this study a clear threshold level can be derived.*

In the first place, taking all the data from the curve-fitting analysis into account, the committee noted a steep concentration-response at the lower-exposure range (see Annex E). Secondly, the observation period was rather short. Since it is known that new cases of allergic sensitisation can occur, even after years of exposure, it is most likely that more cases would have been reported when the observation period had been longer. Taking these considerations into account, the committee decided that no safe threshold level can be derived for TMA, and thus that predefined additional risk levels need to be calculated. Preferably, the committee uses the fitted dose response curve. However, in case of TMA, the variability in the exposure levels corresponding to the lower sensitization risks is high. Therefore, the committee decided to use that concentration as starting point which has a limited variability. From this exposure level, the committee extrapolates linearly to the exposure levels corresponding to the lower additional sensitisation risks. The committee determined an exposure level at which 10% of the occupationally exposed population will get specifically sensitised to TMA as the starting point. This level corresponds to 18 µg TMA/m^3.

The committee uses this level as a starting point for calculating exposure levels at lower additional sensitization risks. The committee takes into account that it is important to protect workers against allergen exposure, because of the everlasting higher risk in developing allergy when sensitised to a specific allergen and because the background incidence in the general population is virtually zero.

Therefore, DECOS calculates additional sensitization risks in humans under workplace exposure conditions of 0.1% to 1%. Using the exposure level of 18 µg TMA/m^3 with an additional risk of sensitisation of 10% as point of departure, 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 over and above the risk of getting sensitised to TMA in the general population. Furthermore, the reference values serve as examples, since also 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."

The uncertainty in the starting point for linear extrapolation is relatively small as a BMDL10% (95% C.I.) of 8 µg TMA/m^3 was derived in the curve fitting analysis of the Grammar data. The BMDU (upper limit of the C.I.) was not presented.

It is noted that the additional risk levels determined by the Health Council of the Netherlands are below the most commonly used occupational exposure limit for TMA across Europe, i.e. 40 µg/m^3.

6.3.3 Evidence that the substance is of equivalent level of concern.

There is ample data on the sensitising properties of TMA due to exposure on the workplace *(summarszed in WHO 2009; Health Council of the Netherlands 2010)*. From the available data it was not possible to derive a no effect level, other than no exposure. All occupational exposures to TMA resulted in an increased risk of sensitisation compared to non-exposed workers. Furthermore, an increase in exposure was associated with an increase in sensitisation.

Table 9 summarises the comparison between CMR substances and TMA regarding seriousness and irreversibility of effects, consequences for society, difficulty in performing a concentration-based risk assessment and quality of life loss.

Table 9: 'Level of concern' comparison between TMA and CMR substances

	Carcinogenic & mutagenic	**Reproductive – development**	**TMA**
Health effects			
Type of probable health effect	Serious and permanent organ dysfunction, inheritable defects and/or death.	Serious and permanent organ dysfunction. Malformations or death in unborn children.	Serious and permanent organ dysfunction. Permanent impairment of lung functions (occupational asthma), rhinitis/ conjunctivitis.
Irreversibility	Effects irreversible	Effects irreversible	Sensitisation is irreversible. TMA may cause permanent impairment of lung function.
Other potential factors			
Social concern	Widespread concern about cancer. Cost implications for society in terms of healthcare.	Widespread concern about adverse effects on children. Cost implications for society in terms of healthcare.	Cost implications for society in terms of healthcare. Associated with disability.
Is a concentration-based risk assessment possible (derivation of a "safe" no effect level)	Depending on the mode of action, for genotoxic carcinogens and mutagens 'zero risk' is only possible when there is no exposure	Yes, from animal experiments it is possible to determine a safe concentration.	No, a validated animal model is not available for the determination of respiratory sensitisation. From the human clinical data of TMA induces occupational asthma, it is not possible to derive a "safe" no effect level for sensitisation.
Quality of life affected	Long-term illness limiting the possibility of living a normal working and private life.	Children with developmental effects may need life-long medication and support in their daily life. Life of parents also affected (emotional investment, care, financial costs).	Long-term illness limiting the possibility of living a normal working life. Requires long-term medication. Re-training of affected staff.

6.3.4 Conclusion on whether the substance gives rise to an 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 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[6]. 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), 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 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

[6] https://www.ser.nl/nl/grenswaarden/trimellietzuuranhydride.aspx access date April 6th 2016.

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 (Art. 57f) 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 57f 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[7] 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.

Conclusion: 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 REACH.

[7] General Court 30 April 2015 T-134/13 on HHPA and T-135/13 on MHHPA.

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