MEMBER STATE COMMITTEE

SUPPORT DOCUMENT FOR IDENTIFICATION OF

HEXAHYDROMETHYLPHTHALIC ANHYDRIDE [1]

(EC number: 247-094-1 and CAS number: 25550-51-0)

HEXAHYDRO-4-METHYLPHTHALIC ANHYDRIDE [2]

(EC number: 243-072-0 and CAS number: 19438-60-9)

HEXAHYDRO-1-METHYLPHTHALIC ANHYDRIDE [3]

(EC number: 256-356-4 and CAS number: 48122-14-1)

HEXAHYDRO-3-METHYLPHTHALIC ANHYDRIDE [4]

(EC number: 260-566-1 and CAS number: 57110-29-9)

AS SUBSTANCES[1] OF VERY HIGH CONCERN BECAUSE, DUE TO THEIR RESPIRATORY SENSITISING PROPERTIES, THEY CAUSE PROBABLE SERIOUS EFFECTS TO HUMAN HEALTH WHICH GIVE RISE TO AN EQUIVALENT LEVEL OF CONCERN TO THOSE OF CMRs AND PBTs/vPvBs

Adopted on 13 December 2012

[1] The individual isomers [2], [3] and [4] (including their cis- and trans- stereo isomeric forms) and all possible combinations of the isomers [1] are covered in this document.

CONTENTS

TABLES

Substance Name(s): hexahydromethylphthalic anhydride [1]

hexahydro-4-methylphthalic anhydride [2]

hexahydro-1-methylphthalic anhydride [3]

hexahydro-3-methylphthalic anhydride [4]

EC Number(s): 247-094-1 [1], 243-072-0 [2], 256-356-4 [3], 260-566-1 [4]

CAS number(s): 25550-51-0 [1], 19438-60-9 [2], 48122-14-1 [3], 57110-29-9 [4]

The following public name is used throughout the dossier: MHHPA (deriving from the name methylhexahydrophthalic anhydride) and covers hexahydromethylphthalic anhydride [1], hexahydro-4-methylphthalic anhydride [2], hexahydro-1-methylphthalic anhydride [3], hexahydro-3-methylphthalic anhydride [4] and all possible combinations of the isomers [1] (including their cis- and trans stereo isomeric forms).

The substances are identified as substances of equivalent concern according to Article 57 (f).

Summary of how the substance(s) meet(s) the CMR (Cat 1A or 1B), PBT or vPvB criteria, or is/are considered to be (a) substance(s) giving rise to an equivalent level of concern

Effects on human health:

Hexahydromethylphthalic anhydride (MHHPA) is covered by index number 607-241-00-6 in Annex VI, part 3 of Regulation (EC) No 1272/2008[2] and classified as respiratory sensitiser, amongst other.

MHHPA is commonly used in a specific mixture with HHPA therefore most studies consider exposure to both HHPA and MHHPA. These studies provide scientific evidence that MHHPA (or mixtures thereof) can induce occupational asthma with initial symptoms such as rhinitis, conjunctivitis, wheezing, cough followed by symptoms such as chest tightness, shortness of breath and nocturnal asthmatic symptoms, with a possible delay of symptoms of up to several years. Exposure to MHHPA (or mixtures thereof) may result in persistent symptoms of respiratory hyper-sensitivity after prolonged exposure. Respiratory diseases including occupational asthma after prolonged exposure to MHHPA (or mixtures thereof) have been recorded, confirming that MHHPA can cause serious and permanent impairment of lung function.

Equivalent concern:

The inherent properties of MHHPA and its isomers give rise to equivalent level of concern because:

- Workers exposed to HHPA, MHHPA and methyl tetrahydro- phthalic anhydride and followed for an average of 33 months in a prospective study showed that:
    - 13% responded positive to IgE in the RAST

[2] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006.

  - 16% responded positive to IgG.
  - The exposures in 3 plants ranged from <1 to 189 µg/m^3 for the substances combined. The highest mean exposure to MHHPA was 12 µg/m^3.

- In a follow-up study, exposure–response relationships for HHPA and MHHPA and the development of specific IgE and IgG antibodies and work-related symptoms were evaluated. There were 154 exposed workers and 57 referents:
  - For the exposed workers, there was high prevalence of sensitization (combined cyclic acid anhydride IgE, 22%; combined IgG, 21%), which correlated with exposure.
  - The air levels ranged from <1 to 94 µg/m3 for HHPA and from <3 to 77 µg/m3 for MHHPA.
  - Atopy and smoking did not increase this risk.
  - Work-related symptoms, such as eye irritation, nose irritation, nose bleeding, and lower airways irritation resulting in symptoms such as dyspnea, wheezing, chest tightness, or dry cough, were more prevalent among the workers compared with the referents.

- Thirty-two workers were investigated in a plant manufacturing light-emitting diodes (LEDs):
  - Eight (25%) of the 32 workers tested had positive HHPA specific IgE, specific IgE reactions to MHHPA were not determined in this study.
  - Five had work-related rhinitis and three with additional conjunctives.
  - The exposure time to onset of symptoms ranged from 1-10 months.
  - Exposure levels ranged from 1.9 – 62.4 µg/m^3 for HHPA and 2.0 – 52.8 µg/m^3 for MHHPA.

The studies show that MHHPA is causing respiratory health effects already at relatively low exposure levels (10-50 µg/m^3). The WHO CICAD document (2009) summarized the available epidemiological data for several cyclic acid anhydrides. The available data (see table 5.2) indicates that MHHPA is among the most potent cyclic anhydrides in the group of cyclic acid anhydrides and can cause severe and irreversible adverse effects on human health.

On the basis of the available data for MHHPA the derivation of a safe concentration is not possible.

Therefore, severe health effects cannot be excluded based on this information. Overall, these findings show that the impacts caused by MHHPA on the health of the affected individuals and on society as a whole, are comparable to those elicited by category 1 carcinogens, mutagens and reproductive toxicants (CMRs), and the substance is considered of very high concern.

In addition to information that leads to this conclusion, it is noted that the exposure levels corresponding to the critical effects observed in humans as reported by the WHO are well below the worst case exposure estimates reported by industry in the REACH registration dossiers that have been submitted for the substance.

Conclusion:

Taking into account all available information on the intrinsic properties of MHHPA and its stereo isomers and their adverse effects, it is concluded that these substances can be regarded as substances for which there is scientific evidence of probable serious effects to human health which gives rise to an equivalent level of concern to those of other substances listed in points (a) to (e) of Article 57 of REACH.

Registration dossier(-s) submitted for the substance: Yes, for CAS numbers 25550-51-0 and 19438-60-9

Justification

1 Identity of the substance and physical and chemical properties

1.1 Name and other identifiers of the substance

The substance hexahydromethylphthalic anhydride (MHHPA) includes specific isomers (EC numbers 243-072-1, 256-356-4 and 260-566-1) with subsequent cis- and trans- stereo isomeric forms. *This dossier covers the individual isomers ([2], [3] and [4] including their cis- and trans- stereo isomeric forms) and all possible combinations of the isomers [1].*

The following public name is used throughout the dossier: MHHPA (deriving from the name methylhexahydrophthalic anhydride) and covers hexahydromethylphthalic anhydride [1], hexahydro-4-methylphthalic anhydride [2], hexahydro-1-methylphthalic anhydride [3], hexahydro-3-methylphthalic anhydride [4] and all possible combinations of the isomers [1] (including their cis- and trans stereo isomeric forms).

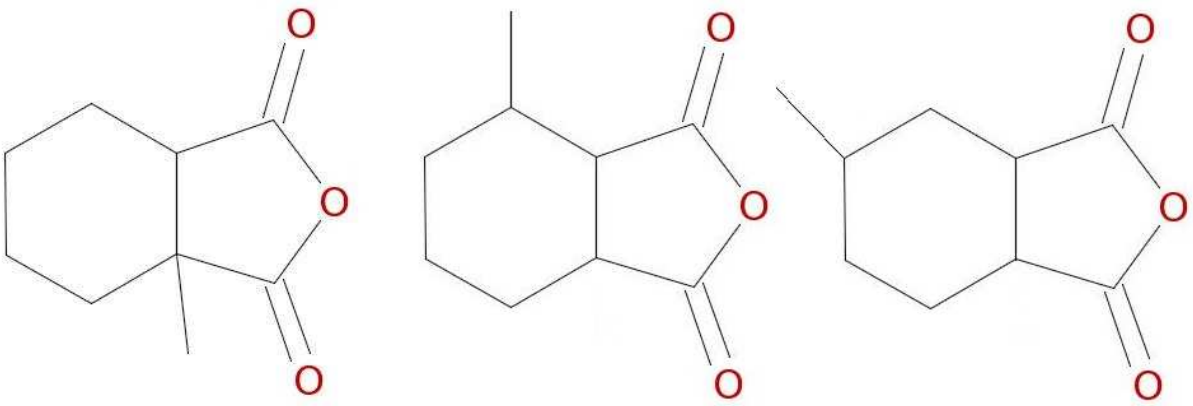
Names of the specific isomers:

Hexahydro-4-methylphthalic anhydride [2]	EC number: 243-072-0 [2]
	CAS number: 19438-60-9 [2]
Hexahydro-1-methylphthalic anhydride [3]	EC number: 256-356-4 [3]
	CAS number: 48122-14-1 [3]
Hexahydro-3-methylphthalic anhydride [4]	EC number: 260-566-1 [4]
	CAS number: 57110-29-9 [4]

Table 1.1: Substance identity of hexahydromethylphthalic anhydride

EC number:	247-094-1
EC name:	hexahydromethylphthalic anhydride
CAS number (in the EC inventory):	25550-51-0
CAS number:	25550-51-0
CAS name:	Methylhexahydrophthalic anhydride
IUPAC name:	Reaction mass of 5-methylhexahydro-2-benzofuran-1,3-dione and 4-methylhexahydro-2-benzofuran-1,3-dione
Index number in Annex VI of the CLP Regulation	607-241-00-6
Molecular formula:	$C_9H_{12}O_3$
Molecular weight range:	168.2
Synonyms:	MHHPA HN-5500 Methylhexahydrophthalic anhydride Hexahydromethylphthalic anhydride 1,3-Isobenzofuranedion, hexahydromethyl

Structural formula:



1.2 Composition of the substance

Name: hexahydromethylphthalic anhydride

Description: The substance hexahydromethylphthalic anhydride (MHHPA) includes specific isomers (EC numbers 243-072-1 [2], 256-356-4 [3] and 260-566-1 [4]) with subsequent cis and trans stereo isomeric forms. This dossier covers the individual isomers ([2], [3] and [4] (including their cis- and trans stereo isomeric forms) and all possible combinations of the isomers [1].

The following public name is used throughout the dossier: MHHPA (deriving from the name methylhexahydrophthalic anhydride) and covers hexahydromethylphthalic anhydride [1], hexahydro-4-methylphthalic anhydride [2], hexahydro-1-methylphthalic anhydride [3], hexahydro-3-methylphthalic anhydride [4] and all possible combinations of the isomers [1] (including their cis- and trans stereo isomeric forms).

Degree of purity: Confidential

Composition: Confidential

Impurities: Confidential

1.3 Physico-chemical properties

Table 1.2: Overview of physicochemical properties of hexahydromethylphthalic anhydride (based on registration)

Property	Value	Remarks
Physical state at 20°C and 101.3 kPa	liquid	
Melting/freezing point	Not determined	Could not be determined.
Boiling point	299 ºC	At 1013 hPa, determined by differential scanning calorimetry
Relative density	1.16 g/cm^3 at 20ºC	
Vapour pressure	0.274-0.33 Pa at 25ºC	0.274 Pa used in CSA. Based on QSAR model, no measurement data available.
Water solubility	Substance reacts (hydrolysis) in contact with water 8.4 g/L at 20 ± 0.5 °C and pH 3.0 (experimental)	Data waiving is applied. Value used in the CSA
Flash point	160ºC at 1013hPa	
Flammability	Non-flammable	Assessment made based on flash point (waiving statement is used).
Self-ignition temperature	470ºC at 1013hPa	
Partition coefficient n-octanol/water (log value)	KOWWIN v. 1.67 2.51-2.59 at 25ºC (Range given for different isomeric forms of MHHPA). LogKow 2.09 at 40ºC pH6.9 (experimental)	LogKow of 2.59 used in CSA LogKow 2.09 used in the CSA
Dissociation constant	4.12-5.79 at 25ºC	4.12 pKa used in CSA.
Viscosity	60 mPa x s at 25ºC	

2 Harmonised classification and labelling

Hexahydromethylphthalic anhydride is covered by index number 607-241-00-6 in Annex VI, part 3 of Regulation (EC) No 1272/2008[3], as follows:

Table 2.1: Classification according to Annex VI, Part 3, 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		Notes	ATP inserted/ ATP Updated
				Hazard Class and Category Code(s)	Hazard Statement Code(s)	Pictogram Signal Word Code(s)	Hazard statement Code(s)		
607-241-00-6	hexahydro-4-methylphthalic anhydride; [1] hexahydromethylphthalic anhydride; [2] hexahydro-1-methylphthalic anhydride; [3] hexahydro-3-methylphthalic anhydride [4]	243-072-0 [1] 247-094-1 [2] 256-356-4 [3] 260-566-1 [4]	19438-60-9 [1] 25550-51-0 [2] 48122-14-1 [3] 57110-29-9 [4]	Eye Dam. 1 Resp. Sens. 1 Skin Sens. 1	H318 H334 H317	GHS08 GHS05 **Dgr**	H318 H334 H317	C	CLP00/

Table 2.2: Classification according to Annex VI, Part 3, Table 3.2 (list of harmonised classification and labelling of hazardous substances from Annex I of Council Directive 67/548/EEC) of Regulation (EC) No 1272/2008

Index No	Chemical name	Notes related to substances	EC No	CAS No	Classification	Labelling
607-241-00-6	hexahydro-4-methylphthalic anhydride; [1] hexahydromethylphthalic anhydride; [2] hexahydro-1-methylphthalic anhydride; [3] hexahydro-3-methylphthalic anhydride [4]		243-072-0 [1] 247-094-1 [2] 256-356-4 [3] 260-566-1 [4]	19438-60-9 [1] 25550-51-0 [2] 48122-14-1 [3] 57110-29-9 [4]	Xi; R41 R42/43	Xn R: 41-42/43 S: (2-)22-24-26-37/39

3 Environmental fate properties

Not relevant for the proposed SVHC identification under Article 57 (f).

4 Human health hazard assessment

See also section 2 on harmonised classification and labelling.

Please note: At this moment, there is no information available to distinguish between the (stereo)isomers of hexahydromethylphthalic anhydride. Most, if not all, study reports that investigated the exposure and/or possible health effects did not specify whether they used the

[3] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006.

specific isomer or mixture of isomers. Unless stated otherwise, it is assumed that the mixture of isomers is considered and results assumed to be valid for all stereoisomers.

Sensitisation

Toxicological mechanism of MHHPA sensitisation

Sensitisation is characterized 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 MHHPA 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 MHHPA 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 MHHPA evokes the classical type I hypersensitivity inflammatory reaction, resulting for example in chronic inflammation of the lungs. This can lead to permanent impairment of the lung (see section 6.3.1.1.; Holgate et al. 1999).

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

For many LMW substances another pathway, 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 and could theoretically be the case for acid anhydrides as well (Sastre et al. 2003). Until now, no evidence have been found that indicates that acid anhydrides can cause occupational asthma through the IgE independent pathway or not. This IgE independent pathway could explain why certain symptomatic subjects did not positively responded to the radioallergosorbent test (RAST) wherein specific IgE levels are quantified, but still may have an immunological driven reaction.

Furthermore, the irritant property of LMW, like MHHPA, 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).

Skin

Information on skin sensitisation by MHHPA in public literature is scarce. MHHPA is classified as a skin sensitiser category 1 according to CLP regulation 1272/2008. Phthalic anhydride (PA) has been classified a moderate skin sensitiser based on animal studies. However, i*n vivo* animal studies conducted to evaluate cytokine production patterns following topical sensitisation to several cyclic anhydrides, including PA but not MHHPA, seem to indicate that the tested substances were negative in inducing type IV contact allergy (WHO, 2009).

One case report suggests that MHHPA can induce type allergic contact dermatitis (type IV hypersensitisation) based on positive reactions in a Patch test. The allergic reaction was confirmed by immunohistochemical and electron microscopic observations, because MHHPA also induced irritation effects in controls that may give similar symptoms. In the patient of the case study a type I hypersensitisation resulting in contact urticaria was observed as well (Kanerva et al. 1997). The skin effects occurred sooner than rhinitis after inhalation in

chamber provocations, which indicates that skin effects may result from inhalation exposure. IgE-mediated contact urticaria is known to be induced by contact or even airborne exposure to cyclic anhydrides (Helaskoski et al. 2009).

For hexahydrophthalic anhydride (HHPA) and MHHPA, one case of contact urticaria due to airborne exposure is described by Kanerva et al.(1999): A 32-year-old atopic man began work as a winder in a plant producing electrical machines. He developed rhinitis and conjunctivitis within a few months, but consulted a doctor no earlier than after 7 years. He had not previously had skin symptoms, but then also developed work-related pruritus and redness on his arms and face, and was referred for further investigation. He came from a workplace where MHHPA and HHPA were used to harden cycloaliphatic and diglycidyl ether of bisphenol A (DGEBA) epoxy resins (ER). A provocation test with MHHPA 1% aq. was positive at 20 min; a provocation test with the hardener (containing 60–72% HHPA according to the material data safety sheet) was negative when it was tested at 1% aq., but when applied undiluted, it provoked whealing[4]. It was concluded that the patient had occupational contact urticaria from MHHPA and HHPA. The patient did not have direct skin contact with MHHPA or HHPA, and the symptoms were evidently due to airborne contact. Investigations showed that he did not have occupational asthma. It was recommended to the worker to change his job.

Jolanki et al. (1987; as cited in WHO 2009) reported on a case of MHHPA–induced contact urticaria in a worker where electronic components were filled with MHHPA–cured epoxy resin.

Tarvainen et al. (1995; as cited in WHO 2009) reported two cases of contact urticaria, one due to MHHPA and the other due to methyl tetrahydrophthalic anhydride. Symptoms of urticaria began 2 months after airborne exposure. Later, conjunctivitis, rhinitis, and asthma symptoms developed. An IgE-mediated allergy was diagnosed by means of skin prick tests and specific IgE antibodies.

Respiratory

MHHPA is classified as a respiratory sensitiser category 1 according to CLP regulation 1272/2008. MHHPA is known to induce IgE-mediated respiratory sensitisation followed by allergic disease (e.g. allergic rhinitis often associated with allergic conjunctivitis and bronchial asthma) as are the cyclic acid anhydrides in general (WHO 2009). The formation of protein adducts is hypothesized to be the first step in sensitisation. The formation has been demonstrated by total protein and albumin adducts of MHHPA and HHPA in the plasma of exposed workers (WHO 2009).

Experiments with sensitized animals have demonstrated the formation of anhydride-specific IgE and IgG antibodies. MHHPA challenges to sensitized animals resulted in obstructive bronchial reactions (WHO 2009). The induction time for positive specific IgE antibodies was 8.8 months (range 1–35 months) when workers exposed to MHHPA, HHPA, and methyl tetrahydrophthalic anhydride (MTHPA) were followed. Inhibition studies and passive transfer studies have supported the specificity of IgE antibodies, but cross-reactivity among some acid anhydrides has been reported (Topping et al., 1986; Welinder & Nielsen, 1991; Drexler et al., 1994; Lowenthal et al., 1994; all cited in WHO 2009).

Specific cases of respiratory allergy for MHHPA alone have not been reported. A probable reason for this observation is that MHHPA is commonly used in a specific mixture with HHPA for technical application reasons (personal communication with industries). For this reason, most studies consider exposure to both HHPA and MHHPA and the effects thereof as to whether the substances can induce type I hypersensitivity reactions, described by cases of

[4] A wheal is a raised, itchy (pruritic) area of skin that is almost always an overt sign of allergy. Wheals reflect circumscribed dermal edema (fluid collection in the layer of skin below the surface). A wheal is a prima facie evidence for an allergic response of the skin. A wheal is also sometimes called a welt and often a hive (MedicineNet.com 2008).

respiratory sensitisation in workers (WHO 2009). Proof of type I hypersensitive reactions are generally obtained by performing a radioallergosorbent test (RAST), wherein specific IgE determinations are made, complemented by skin prick tests and airborne challenges with the substance. Although, the tests themselves do no necessarily indicate the presence of clinical effects, they do indicate that a subject has become sensitized or not to the specific substance. An overview of the cited studies in WHO (2009) are described in more detail below:

Welinder et al. (1994) found that workers exposed to HHPA in electronics industry at levels of <10, 10–50, and >50 µg/m^3 (determined in the period 1989-1990) had developed specific IgE antibodies, but there was no evidence of a consistently increasing exposure-response. The setup of the cross-sectional study may be the cause of the lack of a clear exposure-response. MHHPA is used to a lesser extent, but average exposure levels found were 2 and 48 µg/m^3 in two casting departments, respectively, with a total range of 2-403 µg/m^3. Although the authors restrict their conclusions to HHPA, they do state that a high correlation was found between IgE antibodies to HHPA-HSA (human serum albumin) and MHHPA-HSA (r=0.94) indicating that MHHPA may also be a potent IgE sensitiser and probably cross-reacts with HHPA. Besides the respiratory sensitisation of the subjects, there was no mentioning of clinical effects by the authors.

Tarvainen et al. (1995; as cited in WHO 2009) reported two cases of contact urticaria, one due to MHHPA, the other due to methyl tetrahydrophthalic anhydride. Symptoms of urticaria began 2 months after airborne exposure. Later, conjunctivitis, rhinitis, and asthma symptoms developed. An IgE-mediated allergy was diagnosed by means of skin prick tests and specific IgE antibodies.

Welinder et al. (2001) followed workers exposed to HHPA, MHHPA and methyl tetrahydro-phthalic anhydride for an average of 33 months (range 1–85 months) in a prospective study. The exposures in 3 plants ranged from <1 to 189 µg/m^3 for the substances combined. The highest mean exposure to MHHPA was 12 µg/m^3 in plant 1. The authors did not provide substance specific IgE sensitisation data and argued that combined analyses to the three substances were justified based on animal experimental data showing similar mechanisms, as was shown previously by Topping et al., 1986; Welinder & Nielsen, 1991; Drexler et al., 1994; Lowenthal et al., 1994; all cited in WHO 2009. Thus rather than looking at single substances, the author chose to combine them in the analyses. For all plants combined, 13% responded positive to IgE in the RAST and 16% responded positive to IgG. The authors calculated an increased risk (odds ratio: 3.4 (95% confidence interval 1.2-9.4) when subjects are exposed higher than 15 µg/m^3. Preliminary symptoms reported were eye irritation, nose blockage and running nose, noting that the irritant nature of the cyclic acid anhydrides may have caused the effects as well. Other clinical symptoms were reported in Nielsen et al. (2001).

Nielsen et al. (2001) evaluated the exposure–response relationships for HHPA and MHHPA and the development of specific IgE and IgG antibodies and work-related symptoms in follow-up of the work by Welinder et al. 2001. There were 154 exposed workers and 57 referents in this study of an epoxy resin–using factory. Air levels of these anhydrides were determined by GC-MS. The air levels ranged from <1 to 94 µg/m3 for HHPA and from <3 to 77 µg/m3 for MHHPA. For the exposed workers, there was high prevalence of sensitisation (combined cyclic acid anhydride IgE, 22%; combined IgG, 21%), which correlated with exposure. Atopy and smoking did not increase this risk. Work-related symptoms, such as eye irritation, nose irritation, nose bleeding, and lower airways irritation resulting in symptoms such as dyspnea, wheezing, chest tightness, or dry cough, were also more prevalent among the workers compared with the referents.

Other case reports were found in public literature and in a combined Nordic Exposure Group and Dutch Expert Committee on Occupational standards report (Keskinen 2004). These studies are described below:

Sala et al. (1996) reports on a 40 year old male patient who had laryngitis with specific hypersensitivity to MHHPA. The patient has been exposed for 13 years as an electrician to this substance (no further details given). The patient responded to a provocation tests scoring 2 of

4 in vocal cord status change, responded positive in the skin prick test (+++) and had elevated IgE levels. Another symptom reported was rhinitis.

Yokota, et al. (2002) investigated thirty-two workers in a plant manufacturing light-emitting diodes (LEDs) for portable telephones by questionnaire and serologic investigations. An epoxy resin system with a mixture of HHPA and MHHPA as a hardener was located in three separate sections of the plant where the LEDs were encapsulated in the epoxy resin mixture for protection. The amounts of the hardener used in a month in workplaces A, B, and C were about 1800 kg, about 60 kg, and about 15 kg, respectively. According to the material safety data sheet, the main component in the hardener is HHPA, but MHHPA has also been used as an added ingredient to HHPA. In workplaces A and C, the encapsulation process was made by use of two big enclosed epoxy coating and hardening systems and one small system of that type, respectively. Air of the workplaces was contaminated by the anhydride vapor from the curing ovens (temperature 100–150°C). In workplace B, the encapsulation process consisting of the coating department and the hardening department, it was made by use of five small-enclosed epoxy coating systems, and coated LEDs were transported to curing ovens by workers. Smoke tubes demonstrated visually that air currents from the hardening department flowed to the coating department. All exposed workers were involved in monitoring work, the resin mixing procedure, or both. The subjects completed a questionnaire about symptoms (from the eyes, nose, and lower respiratory tract), their relation to work, atopic history, smoking status, duration of exposure, and occupational history. After that, a physician performed a physical examination and venous blood samples were obtained. Rhinitis, conjunctivitis, or asthma in the workplace more than twice a week, with no complaints at the weekends or during holidays, were considered as indicating work-related symptoms. Eight (25%) of the 32 workers tested had positive HHPA specific IgE, specific IgE reactions to MHHPA were not determined in this study. Five had work related rhinitis and three with additional conjunctives. None of the subjects had yet symptoms of work-related asthma. The exposure time to onset of symptoms ranged from 1-10 months. Exposure levels ranged from 1.9 – 62.4 µg/m^3 for HHPA and 2.0 – 52.8 µg/m^3 for MHHPA.

Jones et al. (2004) investigated the relationschip between genetic susceptibility in the HLA alleles and known cases of HHPA, MHHPA and methyl tetrahydrophthalic anhydride hypersensitisation. The cases were confirmed by skin prick tests and specific nasal challenges. In total 52 cases were selected. Nineteen subjects were exposed previously to low levels, i.e. <10 µg/m^3, 16 subjects to 10-50 µg/m^3 and the remaining subjects were exposed previously to levels exceeding 50 µg/m^3. Further details on symptoms, prevalence values, or substance specific cases were not presented.

Helaskoski et al. (2009) described 21 patients, 16 of whom were previously diagnosed with allergic rhinitis, that were diagnosed with occupational contact urticaria. The subjects were submitted to skin prick tests and specific IgE determinations. The Finnish patients were selected based on occupational medical history (1990-2006). They all worked in the electronics industry as winder, installation worker, production line worker, chimney sweeper, electrician or impregnator. Fifteen patients had come into contact with MHHPA on in the workplace, of which 13 exclusively to MHHPA. Of the latter 13 patients, 10 were diagnosed with anhydride rhinitis and 2 subjects with anhydride asthma of which the specific substance was not identified, but considering the indicated exposure must have been caused by MHHPA. The skin prick tests generally showed that the reaction was highest when challenged with the anhydride used at the workplace, but that other anhydrides also caused positive reactions, indicative of cross-reactions.

Jeppsson et al. (2009) included 12 workers in their 'pilot' study to investigate MHHPA adducted HSA in NAL (nasal lavages) fluids. All workers are employed at a plant manufacturing electrical capacitators using MHHPA in its processes. The workers underwent medical examinations and filled out questionnaires regarding symptoms thought to be work related. Six subjects were sensitized to MHHPA, the other selected workers were not. The exposure at the workplace was considered to be to MHHPA vapours, but was not quantified by measurements. Instead, biomonitoring data from urine was used resulting in an average exposure level of 9 µg/m^3. Of the sensitized subjects, 2 reported to have had nose bleedings and eye and nose symptoms in the past 2 days, against 1 reported nose bleed, 2 reported eye and nose symptoms and 1

lower airways symptom in the non-sensitized subjects. Based on these results the authors stated cautiously that sensitisation and symptoms do not seem to follow a clear dose-response, however mention that the study design is too limited to base conclusions on. The authors continue saying that their findings, i.e. symptoms of eye and nose are more profound than lower airways symptoms and that half of symptomatic subjects are sensitized, were consistent with others (Nielsen et al. 2001; Welinder et al. 1994; 2001).

Cross-reactions with other cyclic acid anhydrides

The number of studies where MHHPA and related health effects were exclusively investigated are scarce. Most of the studies involve co-exposure with other cyclic acid anhydrides such as HHPA. HHPA and MHHPA are closely related structurally and observed health effects are the same showing similar patterns. Rosqvist et al. 2003 seem to show that HHPA and MHHPA have different exposure-response relationships based on the specific IgE response, but mention that the differences may be simply explained by higher IgE responses to MHHPA at already very low exposures compared to HHPA IgE response. The authors further conclude that MHHPA may be more potent than HHPA. In literature, there are a number of examples of cross-reactions within the cyclic acid anhydrides.

Welinder et al. 1994 showed the cross-reactivety between HHPA-HSA and MHHPA-HSA (see above). Hatanaka et al. (1997; as cited in WHO 2009) sensitized rabbits subcutaneously to phthalic anhydride–rat serum albumin (RSA). Anti-phthalic anhydride–RSA IgG was observed in high titres, as were anti-phthalic anhydride–HSA IgG and anti-HSA IgG. The anti-phthalic anhydride–HSA antibodies were cross-reactive with HHPA–HSA, MHHPA-HSA, and methyl tetrahydrophthalic anhydride–HSA. The observations by Helaskoski et al. (2009) in the skin prick tests and IgE determinations show a similar picture. Below the results table (Table 5.1) from Helaskoski et al. was adopted:

Table 4.1: Results of skin prick tests and specific IgE determination (RAST) after challenge with a range of cyclic acid anhydrides for a number of patients that are exposed to one or two anhydrides at the workplace.

		PA		MA		TMA		MHHPA		MTHPA		HHPA		CA	
Patient number	Anhydride used at the workplace	Prick (mm)	IgE (kU/l)	Prick (mm)	IgE (kU/l)	Prick (mm)	IgE (kU/l)	Prick (mm)	IgE (kU/l)	Prick (mm)	IgE (kU/l)	Prick (mm)	IgE (kU/l)	Prick (mm)	IgE (kU/l)
1	MHHPA	9	4.6	8	—	0	—	**28**	**4.5**	9	12.2	33	—	—	—
2	MHHPA	5	8.0	5	1.9	0	<0.3	**11**	—	7	15.1	9	15.5	3	—
3	MHHPA	0	2.3	3	1.2	0	<0.3	**20**	**1.3**	7	5.1	8	5.5	—	—
4	MHHPA	0	—	0	—	0	—	**8**	—	—	—	9	3.15	0	—
5	HHPA, MHHPA	7	14.9	9	—	4	—	**10**	—	10	—	**10**	—	—	—
6	MHHPA	5	0.46	0	—	0	—	**9**	—	7	2.53	6	2.0	0	—
7	MHHPA	0	3.9	0	—	0	—	**10**	**1.7**	6	—	6	4.0	0	—
8	MHHPA	0	0.5	0	—	0	—	**14**	—	—	2.44	18	1.67	0	—
9	MHHPA	0	1.7	3	0.4	0	<0.3	**7**	**2.7**	7	4.4	7	4.1	—	—
10	MHHPA	7	7.2	4	1.0	0	0.5	**20**	**3.3**	25	9.1	40	10.2	—	—
11	MHHPA	9	7.4	8	1.9	4	1.2	**13**	**20.1**	13	14.8	—	—	—	—
12	MHHPA	15	4.0	0	<0.3	4	—	**21**	**3.1**	6	6.3	7	—	—	—
13	MHHPA	11	8.3	6	2.3	6	1.0	**13**	**9.4**	12	18.8	13	14.9	6	—
14	MHHPA	0	1.3	0	<0.3	0	<0.3	**5**	**0.6**	4	2.0	6	—	—	—
15	MHHPA, MTHPA	10	>52.5	9	8.7	7	6.2	**10**	**>52.5**	**9**	**>52.5**	—	—	—	—
16	MTHPA	5	5.1	7	—	5	—	8	—	**10**	**10.2**	10	—	0	—
17	MTHPA	0	<0.3	0	<0.3	0	<0.3	5	<0.3	**8**	**<0.3**	8	—	—	—
18	PA	**6**	**1.4**	0	<0.3	0	<0.3	0	<0.3	0	<0.3	0	—	—	—
19	PA	**4**	**0.7**	0	<0.3	0	<0.3	0	<0.3	0	<0.3	0	<0.3	—	0
20	MA	0	2.4	**14**	**9.4**	0	—	0	—	0	—	0	—	—	—
21	CA	3	1.2	5	1.7	4	<0.3	6	1.1	6	2.9	6	2.4	**10**	**120**

—, not tested; CA, chlorendic anhydride; HHPA, hexahydrophthalic anhydride; IgE, immunoglobulin E; MA, maleic anhydride; MHHPA, methyl hexahydrophthalic anhydride; MTHPA, methyl tetrahydrophthalic anhydride; PA, phthalic anhydride; TMA, trimellitic anhydride.
[a]The anhydride causing the contact urticaria are indicated in bold.

Risk related information

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 induction of 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, which is a concentration level that corresponds to a predefined accepted level of risk of allergic sensitisation (Health Council of the Netherlands 2008).

For HHPA, such a reference value has been recently calculated by the Health Council of the Netherlands (Health Council of the Netherlands 2010). Two studies (Nielsen, et al. 2001; Rosqvist, et al. 2003) on the relationship between exposure to HHPA and specific IgE sensitisation provided a basis for deriving an reference value for respiratory sensitisation. It concerns two different study populations from the same research group, with combined exposure to HHPA and MHHPA, but with data separated for allergic IgE-mediated sensitisation and exposure levels for both HHPA and MHHPA. The Dutch expert Committee on Occupational Safety from the Health Council determined an exposure level at which 10% of the occupationally exposed population will get specifically sensitized to HHPA as the starting point. This level corresponds to 0.73 µg HHPA/m^3. The committee took this level as a starting point for calculating exposure levels corresponding to lower additional sensitisation risks (note that such levels should be compared to a derived minimal effect level, DMEL). The linear model was applied for HHPA, because data that would indicate otherwise are limited. Using the exposure level of 0.73 µg HHPA/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:

• 0.007 µg HHPA/m^3, which corresponds to an additional risk of 0.1% due to occupational exposure, as an 8-hour time weighted average concentration

• 0.07 µg HHPA/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 becoming sensitized to HHPA in the general population. Please note that becoming sensitized does not mean one will suffer from clinical effects. A second or repeated exposure is required to elicit an effect once a subject has become sensitized and at first can be mild. Such effects, however, are likely to progress into more severe effects if exposure is prolonged (see section 6.3.1.1). The Health Council states further that these 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. The Health Council concluded that there was insufficient data available for MHHPA to derive a risk level.

In the registration dossier under REACH, an inhalation long-term derived no effect level (DNEL) of 79.3 mg/m^3 (worker population) for MHHPA is derived based on the oral repeated dose toxicity data. Local irritating and sensitisation effects are not taken into account. Instead, sensitisation is regarded as an effect for which a threshold (no effect) exposure cannot be determined. As a result, a DNEL/DMEL for the hazard respiratory sensitisation is not derived. Although the RCR in the registration dossier is below one, given the high DNEL, this probably does not prevent workers from the risk of respiratory sensitisation. On the contrary, the inhalation exposure estimate of MHHPA in the registration dossier (confidential data) indicates a realistic risk for respiratory sensitisation as increased levels of specific IgE were linked to exposure at workplace at ranges from 10-50 µg/m^3 (see also table 5.2 below), and the additional risk levels derived by the Dutch Health Council are even much lower.

Potency

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. The WHO CICAD document (WHO 2009) summarized the available epidemiological data as follows:

Table 4.2: Critical effects in humans with corresponding exposure levels of cyclic acid anhydrides (adopted from WHO 2009)

Acid anhydride	Exposure level (µg/m^3)	Critical effect	References
Phthalic anhydride	1500–17 400	Sensitization, asthma	Nielsen et al. (1988)
Tetrachlorophthalic anhydride	140–590	Sensitization, work-related asthma symptoms	Liss et al. (1993)
Trimellitic anhydride	10–40	Sensitization, work-related symptoms	Barker et al. (1998)
Hexahydrophthalic anhydride and methyl hexahydrophthalic anhydride	10–50	Sensitization	Welinder et al. (1994)
Methyl tetrahydrophthalic anhydride	5–20	Sensitization, rhinoconjunctivitis, asthma	Nielsen et al. (1992); Yokota et al. (1999)

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.

The available data supposes that HHPA is among the most potent cyclic acid anhydrides in the group of cyclic acid anhydrides. As can be deduced from Table 5.2, it is anticipated by WHO that MHHPA and HHPA have the same potency of inducing respiratory sensitisation, where it should be noted that based on the study by Rosqvist et al. (2003) it seems that MHHPA is more potent than HHPA.

5 ENVIRONMENTAL HAZARD ASSESSEMENT

Not relevant for the proposed SVHC identification under Article 57 (f).

6 Conclusions on the SVHC Properties

6.1 PBT, vPvB assessment

Not relevant for the proposed SVHC identification under Article 57 (f).

6.2 CMR assessment

Not relevant for the proposed SVHC identification under Article 57 (f).

6.3 Substances of equivalent level of concern assessment

MHHPA is covered by index number 607-241-00-6 of Regulation (EC) No 1272/2008 and classified in Annex VI, Part 3, Table 3.1 (list of harmonised classification and labelling of hazardous substances) as respiratory sensitiser (H334: 'May cause allergy or asthma symptoms or breathing difficulties if inhaled'). The corresponding classification in Annex VI, part 3, Table 3.2 (the list of harmonised classification and labelling of hazardous substances from Annex I to Directive 67/548/EEC) of Regulation (EC) No 1272/2008 is respiratory sensitiser (R42/43: 'May cause sensitisation by inhalation and skin contact'.) Section 4 of this report describes several cases of respiratory sensitisation, where symptoms of contact urticaria, rhinitis and one case of occupational asthma due to co-exposure to MHHPA and HHPA was described, indicating the potential of MHHPA to induce respiratory sensitisation.

According to Article 57(f) of the REACH legislation (Regulation (EC) No 1907/2006) the following substances may be included in Annex XIV in accordance with the procedure laid down in Article 58:

- *substances […] which do not fulfil the criteria of points (d) or (e) — for which there is scientific evidence of probable serious effects to human health or the environment which give rise to an equivalent level of concern to those of other substances listed in points (a) to (e) and which are identified on a case-by-case basis in accordance with the procedure set out in Article 59.*

The REACH guidance on the identification of SVHC (http://echa.europa.eu/web/guest/guidance-documents/guidance-on-reach) further elaborates on the identification of a SVHC according to Article 57(f). The following is stated concerning Article 57(f):

The concerns for substances which exhibit carcinogenicity, mutagenicity and reproductive toxicity arise from a number of factors – the seriousness of the effects, the often irreversible nature of the effects, the consequences for society and the difficulty in performing concentration-based risk assessments - should be taken into account when considering whether a substance shows an equivalent level of concern to CMR (cat 1 or 2) substances.

Other effects that are serious could be considered in relation to an equivalent level of concern to CMR, especially if the effects may also be irreversible. Examples of other effects that can be considered to be serious and irreversible in humans are included in the box below:

• *Substance-related deaths.*
• *Major permanent functional changes in the central or peripheral nervous system, including sight, hearing and the sense of smell.*
• *Severe organ damage or major permanent functional changes in other organ systems (for example the lungs).*
• *Consistent changes in clinical biochemistry, haematology or urinalysis parameters which indicate severe and permanent organ dysfunction.*

However, as noted above, indications or confirmation of these serious effects alone are not sufficient for deciding whether the substance is considered to be of equivalent concern and all contributing factors to the observed serious effect(s) need to be considered. Another consideration is whether the risks from the serious effects seen can be adequately addressed by a normal risk assessment or not. If the answer to this is yes, then the substance could probably be managed through other REACH procedures, primarily registration. For example, although e.g. lethality is a serious effect, an equivalent concern should not be generated on the basis of acute lethality alone, as this can usually be adequately addressed by a normal risk assessment methodology. If an Authority has suspicion or concerns that such a substance poses an unacceptable risk, it could be considered to address these through the restrictions procedure. If the answer to the question above is that a normal risk assessment methodology is not adequate, and there is sufficient scientific evidence to conclude that serious effects are probable and that exposure of humans to the chemical is likely to occur under normal conditions of use, then the substance should be considered as being of equivalent concern.

In conclusion, after the interpretation of the legal text and the REACH guidance, the identification of a substance as SVHC based on Article 57(f) requires a case by case approach:

i. Assessment of the hazard properties of the substance and comparison of their potential impact on health and other factors with the impacts potentially elicited by carcinogenic, mutagenic or reprotoxic substances meeting the criteria of Article 57 (a-c)

ii. Evidence that the substance is of equivalent level of concern (by concluding on the results of the comparison of hazard properties and potential impacts described under (i)).

6.3.1 Assessment of the hazard properties

The guidance on the identification of SVHC 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 1A or 1B) 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 sensitizing properties of MHHPA are provided in chapter 4.

6.3.1.1 The seriousness of the effect

The chemical properties of certain substances can possibly lead to health effects, in a part of the exposed population 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 MHHPA, a respiratory sensitiser, serious and permanent organ dysfunction is a possible outcome. MHHPA is known to sensitize subjects at the workplace and is suspected to cause asthma and rhinitis/conjunctivitis 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 simplified represented 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, proinflammatory 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 maybe mild at first, as 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 MHHPA exposure. Acute high exposures may lead to the reactive airways dysfunction syndrome.

The case reports and epidemiology studies in worker populations have shown that health effects such as rhinitis, conjunctivitis and occupational asthma can result from MHHPA exposure. Effects have been so severe that subjects were forced to leave their current job. It is noted that most cases date back to the period 1990-2006, cases that are more recent have not been found in 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.

6.3.1.2 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 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).

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 MHHPA 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 sensitized individual is exposed to MHHPA again, that signs of e.g. asthma, rhinitis and/or conjunctivitis will occur. The sensitized subject may also respond to other acid anhydrides, e.g. HHPA, when cross reactivity has occurred. 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 subjects are exposed. The half-life of IgE immunoglobines can vary between several months to years and in most cases will practically mean that a subject is sensitized for the rest of his life. As already described in section 6.3.1.1, prolonged exposure can lead to permanent lung damage as lung walls are remodelled if the lungs are under continuous stress.

6.3.1.3 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 MHHPA 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 MHHPA 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.

No specific information is available on the prevalence of occupational asthma due to MHHPA exposure alone. There are however 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.

6.3.1.4 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.

In the case of respiratory sensitisers, it is difficult to establish what the threshold dose is for the induction and elicitation phases of response. The derivation of a safe concentration is not routinely possible and any figure derived would be associated with large uncertainty (for details see section 4). 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 sensitized, does not necessarily also protect the already sensitized 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).

For HHPA such a reference value has been recently calculated by the Health Council of the Netherlands (Health Council of the Netherlands 2010). Using the exposure level of 0.73 µg HHPA/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:

- 0.007 µg HHPA/m^3, which corresponds to an additional risk of 0.1% due to occupational exposure, as an 8-hour time weighted average concentration

- 0.07 µg HHPA/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 HHPA in the general population. The Health Council states further that these 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

For MHHPA such a reference value could not be calculated by the Health Council of the Netherlands (Health Council of the Netherlands 2010), since the available data did not allow a scientifically sound derivation of the reference value.

In the registration dossier, an inhalation long term DNEL of 79.3 mg/m^3 is derived based on the oral repeated dose toxicity data. Local irritating and sensitisation effects are not taken into account. Instead, sensitisation is regarded as an effect for which a threshold (no effect) exposure cannot be determined. As a result, a DNEL for the endpoint sensitisation is not

derived. Although the RCR in the registration dossier is below one, given the high DNEL, this probably does not prevent workers from the risk of sensitisation.

6.3.1.5 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 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 sensitized person may still be able to lead a relatively 'normal' life away from the workplace, but consequence of exposure could still be categorized as a 'serious effect', when the changes to his/her quality of life is considered. In the case of MHHPA, permanent impairment of lung function due to MHHPA 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.

6.3.2 Evidence that the substance is of equivalent level of concern

There is limited substance specific data on the sensitizing properties MHHPA due to exposure on the workplace *(summarized 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 (co-)exposures to MHHPA and other cyclic acid anhydrides 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 6.1 summarizes the comparison between CMR substances and MHHPA regarding seriousness and irreversibility of effects, consequences for society, difficulty in performing a concentration-based risk assessment and quality of life loss.

Table 6.1: 'Level of concern' comparison between MHHPA and CMR substances.

	Carcinogenic & mutagenic	**Reproductive – development**	**MHHPA**
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), Minor effects such as rhinitis/ conjunctivitis
Irreversibility	Effects irreversible	Effects irreversible	Sensitisation is irreversible. MHHPA 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, imminent change in job.
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, no validated animal model is available for the determination of respiratory sensitisation. From the human clinical data of MHHPA induces occupational asthma, it is not possible to derive a "safe" no effect level for sensitisation. Every level of exposure to MHHPA was associated with an increased risk of 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.

6.3.3 Conclusion on the identification of equivalent level of concern

Effects on human health:

Hexahydromethylphthalic anhydride (MHHPA) is covered by index number 607-241-00-6 in Annex VI, part 3 of Regulation (EC) No 1272/2008[6] and classified as respiratory sensitiser, amongst other.

MHHPA is commonly used in a specific mixture with HHPA therefore most studies consider exposure to both HHPA and MHHPA. These studies provide scientific evidence that MHHPA (or mixtures thereof) can induce occupational asthma with initial symptoms such as rhinitis, conjunctivitis, wheezing, cough followed by symptoms such as chest tightness, shortness of breath and nocturnal asthmatic symptoms, with a possible delay of symptoms of up to several years. Exposure to MHHPA (or mixtures thereof) may result in persistent symptoms of respiratory hyper-sensitivity after prolonged exposure. Respiratory diseases including occupational asthma after exposure to MHHPA (or mixtures thereof) have been recorded, confirming that MHHPA can cause serious and permanent impairment of lung function.

Equivalent concern:

The inherent properties of MHHPA and its isomers give rise to equivalent level of concern because:

- Workers exposed to HHPA, MHHPA and methyl tetrahydro- phthalic anhydride and followed for an average of 33 months in a prospective study showed that:
    - 13% responded positive to IgE in the RAST
    - 16% responded positive to IgG.
    - The exposures in 3 plants ranged from <1 to 189 µg/m^3 for the substances combined. The highest mean exposure to MHHPA was 12 µg/m^3.
- In a follow-up study, exposure–response relationships for HHPA and MHHPA and the development of specific IgE and IgG antibodies and work-related symptoms were evaluated. There were 154 exposed workers and 57 referents:
    - For the exposed workers, there was high prevalence of sensitization (combined cyclic acid anhydride IgE, 22%; combined IgG, 21%), which correlated with exposure.
    - The air levels ranged from <1 to 94 µg/m3 for HHPA and from <3 to 77 µg/m3 for MHHPA.
    - Atopy and smoking did not increase this risk.
    - Work-related symptoms, such as eye irritation, nose irritation, nose bleeding, and lower airways irritation resulting in symptoms such as dyspnea, wheezing,

[6] Regulation (EC) No 1272/2008 of the European Parliament and of the Council of 16 December 2008 on classification, labelling and packaging of substances and mixtures, amending and repealing Directives 67/548/EEC and 1999/45/EC, and amending Regulation (EC) No 1907/2006.

chest tightness, or dry cough, were more prevalent among the workers compared with the referents.

- Thirty-two workers were investigated in a plant manufacturing light-emitting diodes (LEDs):
    - Eight (25%) of the 32 workers tested had positive HHPA specific IgE, specific IgE reactions to MHHPA were not determined in this study.
    - Five had work-related rhinitis and three with additional conjunctives.
    - The exposure time to onset of symptoms ranged from 1-10 months.
    - Exposure levels ranged from 1.9 – 62.4 µg/m^3 for HHPA and 2.0 – 52.8 µg/m^3 for MHHPA.

The studies show that MHHPA is causing respiratory health effects already at relatively low exposure levels (10-50 µg/m^3). The WHO CICAD document (2009) summarized the available epidemiological data for several cyclic acid anhydrides. The available data (see table 5.2 in reference 1. Support document for MHHPA, MSC 14 Dec. 2012) indicates that MHHPA is among the most potent cyclic anhydrides in the group of cyclic acid anhydrides and can cause severe and irreversible adverse effects on human health.

On the basis of the available data for MHHPA the derivation of a safe concentration is not possible.

Therefore, severe health effects cannot be excluded based on this information. Overall, these findings show that the impacts caused by MHHPA on the health of the affected individuals and on society as a whole, are comparable to those elicited by category 1 carcinogens, mutagens and reproductive toxicants (CMRs), and the substance is considered of very high concern.

In addition to information that leads to this conclusion, it is noted that the exposure levels corresponding to the critical effects observed in humans as reported by the WHO are well below the worst case exposure estimates reported by industry in the REACH registration dossiers that have been submitted for the substance.

Conclusion:

Taking into account all available information on the intrinsic properties of MHHPA and its stereo isomers and their adverse effects, it is concluded that these substances can be regarded as substances for which there is scientific evidence of probable serious effects to human health which gives rise to an equivalent level of concern to those of other substances listed in points (a) to (e) of Article 57 of REACH.

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