ECHA
EUROPEAN CHEMICALS AGENCY

MEMBER STATE COMMITTEE

SUPPORT DOCUMENT FOR IDENTIFICATION OF

CYCLOHEXANE-1,2-DICARBOXYLIC ANHYDRIDE [1]

(EC Number: 201-604-9 and CAS Number: 85-42-7)

CIS-CYCLOHEXANE-1,2-DICARBOXYLIC ANHYDRIDE [2]

(EC Number: 236-086-3 and CAS number: 13149-00-3)

TRANS-CYCLOHEXANE-1,2-DICARBOXYLIC ANHYDRIDE [3]

(EC NUMBER: 238-009-9 and CAS number: 14166-21-3)

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 cis-HHPA [2] and trans-HHPA [3] isomer substances and all possible combinations of the cis- and trans-isomers of HHPA [1] are covered in the document.*

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Substance Name(s): cyclohexane-1,2-dicarboxylic anhydride [1], cis-cyclohexane-1,2 dicarboxylic anhydride [2], trans-cyclohexane-1,2-dicarboxylic anhydride [3]

EC Number(s): 201-604-9 [1], 236-086-3 [2], 238-009-9 [3]

CAS number(s): 85-42-7 [1], 13149-00-3 [2], 14166-21-3 [3]

The following public name is used throughout the dossier: HHPA (deriving from the name hexahydrophthalic anhydride) and covers cyclohexane-1,2-dicarboxylic anhydride [1], cis-cyclohexane-1,2 dicarboxylic anhydride [2], trans-cyclohexane-1,2-dicarboxylic anhydride [3] and all possible combinations of the cis- and trans-isomers [1].

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:

HHPA is covered by index number 607-102-00-X in Annex VI, part 3 of Regulation (EC) No 1272/2008[2] and classified as respiratory sensitiser, amongst other.

There is scientific evidence that HHPA 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 HHPA may result in persistent symptoms of respiratory hyper-sensitivity after prolonged exposure. Respiratory diseases including occupational asthma after prolonged exposure to HHPA have been recorded in several studies, confirming that HHPA can cause serious and permanent impairment of lung function.

Equivalent concern:

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

- A cross-sectional study of twenty-seven workers carried out in a plant manufacturing bushings for electrical transformers showed that:
    - Four workers (15%) reported occupational asthma, two also reported nocturnal cough, shortness of breath, or wheezing.
    - All four asthmatic workers also developed occupationally related rhinitis and conjunctivitis.
    - Eighteen of the remaining 23 workers reported nasal and/or ocular symptoms while they were at work.

[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.

- Exposure levels ranged from 1.9 mg/m^3 (range 0.6–3.1 mg/m^3) to 3.8 mg/m^3 (range 1.3–8.2 mg/m^3). Three of the workers with occupational asthma worked in the lower exposure area, the other one in both the higher and lower exposure area.

- A study was performed in a plant producing capacitors, fixed and isolated with epoxy resin with HHPA and MHHPA as hardeners:
  - 154 workers exposed to HHPA and MHHPA were examined. As a reference group 57 subjects were recruited with no heavy exposure to sensitizing or irritating agents.
  - For the work-related symptoms, ~ 28% of the workers had symptoms of the nose (blocked, itchy, or running or attacks of sneezing or bleeding),
  - 23% had symptoms of the eyes (lacrimation, itching, scratching, smarting, or burning eyes),
  - 12% reported symptoms of the lower airways (dyspnea, wheezing, chest tightness, or dry cough), and 8% had nose bleeds.
  - Exposure levels of HHPA ranged from <1 µg/m^3 to 94 µg/m^3, for MHHPA exposure levels ranged from <3 µg/m^3 to 77 µg/m^3.
- Thirty-two workers were investigated in a plant manufacturing light-emitting diodes (LEDs), using both HHPA and MHHPA.
  - Eight (25%) of the 32 workers tested had positive HHPA specific IgE.
  - Five had work-related rhinitis and three with additional conjunctivitis.
  - 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.
- A total of 31 sensitized and non-sensitized workers exposed to HHPA were included in a case control study.
  - Twenty of the subjects (65%) complained of work-related nasal symptoms, of those twenty subjects, eleven workers were sensitized against HHPA.
  - Eleven workers (35%) were not sensitized and displayed no work-related symptoms.
- A prospective cohort study was performed in 66 individuals (follow up time between 1 and 7 years) hired at a facility requiring HHPA for its manufacture. At their date of hire, none of the study population had previous exposure to acid anhydrides, and none had antibody against HHPA conjugated to human serum albumin (HHPA-HSA).
  - Three newly hired individuals developed occupational asthma due to HHPA exposure.
  - The three employees who developed occupational asthma had worn respirators ever since they started their employment.

  - Exposure measurements had been taken in the breathing zone of worker, however the level of exposure was uncertain.

- In two follow-up studies, workers previously diagnosed with occupational allergic rhinitis, asthma, haemorrhagic rhinitis or a combination thereof due to HHPA exposure were examined one year later. In the meantime they were all removed from exposure. In total 44 workers were followed of which:
  - nine had asthma alone,
  - ten had haemorrhagic rhinitis alone,
  - four had both,
  - 13 had allergic rhinitis alone,
  - four had both asthma and allergic rhinitis,
  - four had haemorrhagic rhinitis and allergic rhinitis and
  - after removal from exposure (one year), all lung function tests were normal in all workers indicating no permanent damage, however one subject experienced symptoms for more than one year after being exposed. Permanent disability from asthma was reported to be probably related to more than two years of exposure where abnormal pulmonary functions at the time exposure ended was observed in the individuals.

The studies show that HHPA 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 HHPA 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 HHPA 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 HHPA 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 HHPA, cis-HHPA and trans-HHPA 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 humans 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

Justification

1 Identity of the substance and physical and chemical properties

1.1 Name and other identifiers of the substance

Depending on the concentration of the isomers the substance cyclohexane-1,2-dicarboxylic anhydride might be regarded as a mono- or multi-constituent substance. *This dossier covers the individual cis- [2] and trans- [3] isomer substances and all possible combinations of the cis- and trans-isomers [1].* The following public name is used throughout the dossier: HHPA (deriving from the name hexahydrophthalic anhydride) and covers cyclohexane-1,2-dicarboxylic anhydride [1], cis-cyclohexane-1,2 dicarboxylic anhydride [2], trans-cyclohexane-1,2-dicarboxylic anhydride [3] and all possible combinations of the cis- and trans-isomers [1].

Table 1.1: Substance identity of cyclohexane-1,2-dicarboxylic anhydride [1]

EC number:	201-604-9
EC name:	cyclohexane-1,2-dicarboxylic anhydride
CAS number (in the EC inventory):	85-42-7
CAS number:	85-42-7 95327-28-9 102483-85-2 109265-67-0 117276-22-9
CAS name:	1,3-isobenzofurandione, hexahydro-
IUPAC name:	hexahydro-2-benzofuran-1,3-dione
Index number in Annex VI of the CLP Regulation	607-102-00-X
Molecular formula:	$C_8H_{10}O_3$
Molecular weight range:	154.2
Synonyms:	HHPA Hexahydro-isobenzofuran-1,3-dione Hexahydrophthalic anhydride Cyclohexane-1,2-dicarboxylic anhydride 1,3-Isobenzofurandione, hexahydro- 1,2-Cyclohexanedicarboxylic Anhydride

Table 1.2: Substance identity of *cis*-cyclohexane-1,2-dicarboxylic anhydride [2]

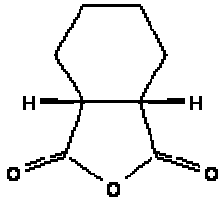
EC number:	236-086-3
EC name:	cis-cyclohexane-1,2-dicarboxylic anhydride
CAS number (in the EC inventory):	13149-00-3
CAS number:	13149-00-3 111720-41-3 127946-28-5 201815-17-0 279240-32-3 634193-83-2 743438-36-0
CAS name:	1,3-Isobenzofurandione, hexahydro-, (3aR,7aS)-rel-
IUPAC name:	(3aR,7aS)-Hexahydro-2-benzofuran-1,3-dione
Index number in Annex VI of the CLP Regulation	607-102-00-X
Molecular formula:	$C_8H_{10}O_3$
Molecular weight range:	154.2
Synonyms:	cis-1,2-Cyclohexanedicarboxylic anhydride Hexahydro-2-benzofuran-1,3-dione, cis

Table 1.3: Substance identity of *trans*-cyclohexane-1,2-dicarboxylic anhydride [3]

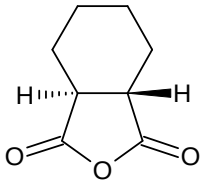
EC number:	238-009-9
EC name:	trans-cyclohexane-1,2-dicarboxylic anhydride
CAS number (in the EC inventory):	14166-21-3
CAS number:	14166-21-3 97233-90-4 128049-67-2
CAS name:	1,3-Isobenzofurandione, hexahydro-, (3aR,7aR)-rel-
IUPAC name:	(3aR*,7aR*)-Hexahydro-2-benzofuran-1,3-dione
Index number in Annex VI of the CLP Regulation	607-102-00-X
Molecular formula:	$C_8H_{10}O_3$
Molecular weight range:	154.2
Synonyms:	trans-Cyclohexane-1,2-dicarboxylic anhydride Hexahydro-2-benzofuran-1,3-dione, trans

Structural formula:

cis-HHPA



trans-HHPA



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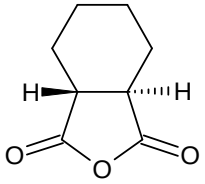

1.2 Composition of the substance

Name: cyclohexane-1,2-dicarboxylic anhydride [1], *cis*-cyclohexane-1,2-dicarboxylic anhydride [2], *trans*-cyclohexane-1,2-dicarboxylic anhydride [3]

Description: mono or multi constituent substance (depending on the concentration of the isomers present)

Degree of purity: Confidential

Composition: Confidential

Impurities: Confidential

1.3 Physico-chemical properties

Table 1.4: Overview of physicochemical properties of cyclohexane-1,2-dicarboxylic anhydride (based on registration).

Property	Value	Remarks
Physical state at 20°C and 101.3 kPa	organic, white compact solid, having the odour characteristic of aromatic compounds	**Value used for CSA:** solid Physical appearance has been investigated according to OPPTS test methods. The substance is an organic, white compact solid, having the odour characteristic of aromatic compounds.
Melting/freezing point	31.9 °C	**Value used for CSA:** 31.9 °C at 1013 hPa Melting point has been investigated according to OECD/EU test methods and determined to be 31.9 °C.
Boiling point	290.6 °C at 1013 hPa	**Value used for CSA:** 290.6 °C at 1013 hPa Boiling point has been investigated according to OECD/EU test methods and determined to be 290.6 °C at 1013 hPa.
Vapour pressure	77 Pa at 20°C and 93 Pa at 25°C	**Value used for CSA:** 93 Pa at 25 °C Vapour pressure has been investigated using a static vapour pressure balance in accordance with OECD/EU test methods. HHPA was determined to have a vapour pressure of 77 Pa at 20°C and 93 Pa at 25°C.
Water solubility	4.2 g/L at 20°C and pH 2.9	**Value used for CSA:** 4.2 g/L at 20 °C Water solubility has been investigated in accordance with OECD/EU test methods and determined to be 4.2g/Lat 20°C and pH 2.9
Partition coefficient n-octanol/water (log value)	(Log10): 1.59	**Value used for CSA:** Log Kow (Pow): 1.59 at 40 °C Partition coefficient has been investigated in accordance with OECD/EU test methods and determined to be 1.59 (Log10 Pow).
Dissociation constant	pKa1 = 4.14 and pKa2 = 6.52	**Value used for CSA:** pKa at 20°C: 4.14 The dissociation constants in water of the di-acid degradation product of the substance has been investigated according to OECD test methods. Values, at 20°C, were determined to be: pKa1 = 4.14 and pKa2 = 6.52.

2 Harmonised classification and labelling

HHPA is covered by index number 607-102-00-X 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 Codes	Pictogram, Signal Word Code(s)	Hazard statement Code(s)		
607-102-00-X	cyclohexane-1,2-dicarboxylic anhydride; [1] *cis*-cyclohexane-1,2-dicarboxylic anhydride; [2] *trans*-cyclohexane-1,2-dicarboxylic anhydride [3]	201-604-9 [1] 236-086-3 [2] 238-009-9 [3]	85-42-7 [1] 13149-00-3 [2] 14166-21-3 [3]	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
607-102-00-X	cyclohexane-1,2-dicarboxylic anhydride; [1] *cis*-cyclohexane-1,2-dicarboxylic anhydride; [2] *trans*-cyclohexane-1,2-dicarboxylic anhydride [3]	C	201-604-9 [1] 236-086-3 [2] 238-009-9 [3]	85-42-7 [1] 13149-00-3 [2] 14166-21-3 [3]	Xi; R41 R42/43	Xn R: 41-42/43 S: (2-)23-24-26-37/39

3 Environmental fate properties

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

4 Human health hazard assessment

Please note: in this section the following public name is used: HHPA (deriving from the name hexahydrophthalic anhydride) and covers cyclohexane-1,2-dicarboxylic anhydride [1], cis-

[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.

cyclohexane-1,2 dicarboxylic anhydride [2], trans-cyclohexane-1,2-dicarboxylic anhydride [3] and all possible combinations of the cis- and trans-isomers [1].

See also section 2 on harmonised classification and labelling.

Sensitisation

Toxicological mechanism of HHPA 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 HHPA 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 HHPA 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 HHPA 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 HHPA, 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. (2009) 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 HHPA, 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

HHPA was found to be a skin sensitiser in a Guinea pig maximization test (European Chemicals Bureau 2000). 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 HHPA, seem to indicate that the tested substances were negative in inducing type IV contact allergy (WHO, 2009).

IgE-mediated contact urticaria is known to be induced by contact or even airborne exposure to cyclic anhydrides (Helaskoski, Kuuliala et al. 2009). For HHPA, one case of contact urticaria

due to airborne epxosure is described by Kanerva, Alanko 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 were methylhexahydrophthalic anhydride (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. Specific IgE for MHHPA was measured, but could not be detected for HHPA. It was concluded that the patient had occupational contact urticaria from HHPA and MHHPA. 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 that he change his *job.*

Respiratory

Experiments with sensitized animals have demonstrated the formation of anhydride-specific IgE and IgG antibodies. HHPA challenges to sensitized animals resulted in obstructive bronchial reactions (Zhao, Zhang et al. 1997)

HHPA is known to induce IgE-mediated respiratory sensitisation followed by allergic disease in the upper and lower airways (e.g. allergic rhinitis often associated with allergic conjunctivitis and bronchial asthma) (summarized in WHO 2009; Health Council of the Netherlands 2010).

Case reports

Chee, Lee et al. (1991) reported a case of occupational asthma due to HHPA exposure. The patient showed a bronchoconstrictive response to a specific inhalation challenge with HHPA. The patient is a 43 old man, a lifelong non-smoker, with a history of childhood asthma and atopy. He had been free of asthmatic attacks for more than 20 years until his present illness. The patient worked as a laboratory technician in a factory manufacturing coating chemicals. The factory produces a two component epoxy based chemical designed for the encapsulation of optoelectronic displays and components. The product is a liquid and comes in part A (epoxy resin) and part B (curing agent containing up to 70% HHPA). The HPPA (98% pure) is heated to 70ºC to liquefy it (in sealed drums). The liquid HHPA is pumped into a tank where it is blended with other additives. The blended mixture (part B) is put into plastic bottles and sealed under nitrogen. The patients job involved, among other, taking samples of part B for quality checks in the laboratory where the samples were heated in a fume cupboard for 10 to 15 minutes. The patient noted that he tended to develop symptoms whenever these processes with HHPA were carried out. Several months after starting the job, the patient began to experience cough, wheezing and chest tightness that required inhaled and oral salbutamol for relief. The symptoms usually occurred after five minutes of exposure and would last up to seven hours unless relieved by medicine. The patient also experienced nocturnal attacks of breathlessness during the course of the working week. Symptoms improved when away from work, on weekends and during vacations. After bronchial provocation to a tin of heated HHPA for 10 minutes, the patient experienced cough, lacrimation and chest tightness, with a rhonchi heard in the lungs. Peak expiratory flow rates (PEFR) fall by 54% and the patient required two doses of ventolin nebulisation for relief of his breathlessness. The patient remained relatively comfortable until six hours later when he again experienced breathlessness with rhonchi heard in the lungs, his PEFR fall with 69%. Nebulised ventolin was administrated and relieved the symptoms. Sixteen hours later the patient was awakened in the middle of the night with a severe asthmatic attack unable to record his PEFR. Again, medicine was administrated to relief the symptoms. Several days after the challenge testing, the patient was again admitted to medical attention with poor control of his asthmatic symptoms and required systemic corticosteroids for control of his asthma. No information is available on possible exposure levels to HHPA.

Case control study

Nielsen, Welinder et al. (1994) performed a study investigating the pathogenic relevance of specific IgE serum antibodies for nasal symptoms. A total of 31 sensitized and non-sensitized workers exposed tot HHPA were included in this study. All of them were working in a plant producing components for the electronics industry. Twenty of the subjects complained of work-related nasal symptoms, of those eleven workers were sensitized against HHPA. Eleven workers were not sensitized and displayed no work-related symptoms. They were matched to the other subjects with regard to sex, age and smoking habits. The nasal challenge consisted of an isotone solution containing HHPA-HSA conjugate (in three increasing concentrations) which was sprayed in the nasal cavity. Nasal symptoms that were recorded included blockage, secretion and a number of sneezes. Furthermore, nasal inspiratory peak flow and nasal lavage was performed. The nasal lavage was analysed for total eosinophils and differential counts of eosinophil, neutrophil and epithelial cells. In the IgE-sensitized group, the challenge induced a clear-cut and rapid increase of nasal symptoms in all subjects, which persisted for at least two hours. The response was variable in intensity amongst the subjects. There was also a decrease in nasal inspiratory peak flow. In the two non-sensitized (with and without work-related nasal symptoms) groups, no significant reaction was seen. Moreover, in the sensitized group, a significant increase of tryptase in lavage fluid was found after challenge. Tryptase is selectively found in the mast-cell granulae and is thus considered to be a marker for the mast cell mediated response. Analyses of the lavage fluid showed a significant increase in total eosinophils and the differential count of eosinophil and neutrophil cells of the sensitized group compared to the non-sensitized group. The number of epithelial cell showed a significant decrease in the sensitized group.

Cross sectional studies

Moller, Gallagher et al. (1985) performed a study under twenty-seven workers in a plant manufacturing bushings for electrical transformers. An epoxy resin system with HHPA as a reagent was located in one section of the plant where crystalline HHPA was liquefied by heating. Workers were studied by questionnaire, pulmonary function tests and serologic investigations. The questionnaire was used to evaluate workers' respiratory and ocular complaints. The diagnosis of a history of asthma was made on the basis of symptoms of shortness of breath, wheezing, or coughing. Specification of occupational asthma required additional criteria of unequivocal exacerbation at work and/or nocturnal symptoms, improvement away from the workplace, and a negative history of asthma before occupational exposure. A diagnosis of rhinitis was made if a worker noted rhinorrhea, nasal congestion and/or sneezing. Conjunctivitis was determined by the presence of ocular itching, burning, or tearing of the eyes. Occupational rhinitis and/or conjunctivitis required the presence of symptoms only at work. Four workers (15%) reported occupational asthma, two also reported nocturnal cough, shortness of breath, or wheezing. All four asthmatic workers also developed occupationally related rhinitis and conjunctivitis. Eighteen (78%) of the remaining 23 workers reported nasal and/or ocular symptoms while they were at work. Pulmonary function testing on the 27 workers demonstrated no significant post-shift decrement of forced expiration volume (FEV) when results were compared to pre-shift test results. Exposure levels ranged from 1.9 mg/m^3 (range 600–3100 µg/m^3) in the low exposed area to 3.8 mg/m^3 (range 1.3–8.2 mg/m^3) in the high exposed area. Three of the workers with occupational asthma worked in the lower exposure area, the other one in both the higher as lower exposure area.

Grammer, Shaughnessy et al. (1993) conducted a surveillance study of approximately 50 workers in a plant manufacturing insulators for electrical equipment. Clinical evaluation was performed using an occupational respiratory questionnaire, pulmonary function tests, chest radiograph, and serologic assays. Any individual having an abnormality of any of the above parameters was interviewed and examined. In this report, the authors focus on the occurrence of rhinitis, nasal erosion and epistaxis. In total six workers were diagnosed with occupational rhinitis, nasal erosion and epistaxis, with removal of exposure the erosions and epistaxis resolved. Three workers also had symptoms, interval pulmonary function tests, and physical findings consistent with asthma. Results of annual baseline pulmonary function tests and chest radiographs were normal in all individuals. No exposure levels are known.

Prospective cohorts

Grammer, Harris et al. (2002) performed a prospective cohort study in 66 individuals (follow up time between 1 and 7 years) hired at a facility that makes an epoxy resin product requiring HHPA for its manufacture. In this work process, there are many curing oven machines. Part A and part B of an epoxy resin are piped into the mold of the curing oven machine in proper proportions. The mixture is heated for a predetermined amount of time. At time when the mixture should be a solid epoxy resin product, the operator opens the mold. Rarely, the mixture does not cure properly; then, when the mold is opened, HHPA fumes emanate. At their date of hire, none of the study population had previous exposure to acid anhydrides, and none had antibody against HHPA conjugated to human serum albumin (HHPA-HSA). Each individual was annually evaluated with a questionnaire, spirometry, and serology for IgG and IgE against HHPA-HSA. Any individuals who had abnormal spirometry, respiratory symptoms on questionnaire, or positive serologic findings were interviewed, examined, and skin tested with HHPA-HSA. Spirometry was performed annually for all exposed employees and as needed to evaluate employees who developed respiratory symptoms related to work. Criteria for diagnosis of immunologic respiratory disease due to HHPA are shown in table 4.1.

Table 4.1: Criteria for IgE- or IgG-Mediated Respiratory Disease due to HHPA (adapted from Grammer, Harris et al. 2002)

	IgE-Associated Diseases		IgG-Associated Disease
Variables	Allergic Rhinitis	Asthma	Hemorrhagic Rhinitis
Symptoms	Compatible symptoms, including one or more of the following: nasal congestion, pruritus, rhinorrhea, sneezing	Compatible symptoms, including one or more of the following: cough, dyspnea, wheeze, chest tightness	History of significant epistaxis
Signs	Bogginess, edema, erythema of nasal mucosa	Wheeze, prolonged expiratory phase	Nasal erosions
Spirometry	NA	> 15% change FEV_1 at work vs away for 1 week	NA
Chest radiograph	NA	Normal	NA
Antibody	IgE antibody against HHPA-HSA	IgE antibody against HHPA-HSA	IgG antibody against HHPA-HSA

Three newly hired individuals developed occupational asthma due to HHPA exposure (Grammer, Harris et al. 2002). The time to development of occupational asthma in these three individuals was 3, 4, and 5 years, respectively. The three employees who had occupational asthma develop had worn respirators ever since they started their employment. Exposure measurements have been taken in the breathing zone of worker. Unfortunately, there seem to be a typo in the report as the corresponding table reads a mean HHPA concentration of 0.635 mg/m^3 with a range of 0.0028-0.2500 mg/m^3. It is not clear whether the mean concentration contains an error or the maximum concentration measured. These are concentrations of airborne HHPA to which an employee would be exposed without benefit of a respirator. In the study of Grammer, Harris et al. approximately 363 person-working years were followed in which workers are at risk of occupational asthma. In this time period, three new cases of occupational asthma developed. This would correspond to an estimated incidence rate of occupational asthma due to HHPA exposure of 8 per 1.000 person-working years in this particular working environment. This number should be interpreted with caution, as no underlying data on the amount of working hours per person was available. It is assumed that every worker participated in this study worked the same amount of time.

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). Of the 21 subjects, only one worker had exposures to HHPA and was co-exposed to MHHPA. His profession was winder at an electronics industry. The subject scored positively in the RAST for both MHHPA and HHPA and similarly the skin prick test was also positive for both substances. The subjects showed symptoms of anhydride rhinitis. 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.

Follow up studies after removal of exposure

In two studies by Grammer et al. (Grammer, Shaughnessy et al. 1995; Grammer and Shaughnessy 1996) workers previously diagnosed with occupational allergic rhinitis, asthma, heamorrhagic rhinitis or a combination thereof due to HHPA exposure were examined in a follow-up a year later. In the meantime they were all removed from exposure. In total 44 workers were followed of which nine had asthma alone, ten had heamorrhagic rhinitis alone, four had both, 13 had allergic rhinitis alone, four had both asthma and allergic rhinitis and four had heamorrhagic rhinitis and allergic rhinitis. In one case of asthma, symptoms were not disappeared after a year of no exposure. The worker stated that he had shortness of breath and occasional wheezing. His physician had prescribed inhaled albuterol (four times daily) and inhaled ipratropium bromide (four times daily). All lung function tests were normal in all workers indication no permanent damage. However, only two employees experienced symptoms for more than one year at time of exposure. In other studies reporting permanent disability from asthma, those most likely to be affected were workers who had symptoms for more than two years and who had abnormal pulmonary functions at time of removal (Chan-Yeung and Malo 1993 cited in Grammer, Shaughnessy et al. 1995).

National Occupational Diseases Registry data

Most national occupational disease registries usually do not register the specific casual agent of occupational diseases but use a class of substances instead. In the UK, there have been nine actual cases of occupational asthma attributed to the cyclic anhydrides reported to SWORD (1989-2011). One case was attributed specifically to HHPA whilst the remaining eight diagnoses were attributed to 'phthalic anhydrides'. These cases were reported under the occupations of painters, welders, assemblers, engineers, resin manufacture, treatment operators and 'enzymes'. There have been a further eight actual cases reported to SWORD where the agent has been recorded simply as 'anhydride' or 'acid anhydride'. There has been one case of occupational asthma attributed to phthalic anhydride in a 58 year old male working in insulator manufacture reported in 1996 to OPRA (1996-2011). A further case was attributed to 'acid anhydride' (The Health and Occupation Reporting network (THOR) 2012).

Supporting evidence of mixed exposure to HHPA and other cyclic anhydrides

Nielsen, Welinder et al. (2001) performed a study in a plant that produces capacitors, fixed and isolated with epoxy resin with HHPA and MHHPA as hardeners. Altogether 154 workers exposed to HHPA and MHHPA were examined. As a reference group 57 subjects were recruited from two mechanical industries in the same area, with no heavy exposure to sensitizing or irritating agents. Extensive occupational and medical histories were obtained by a questionnaire. Current and previous work tasks in the present workplace were recorded, as were symptoms of the eyes (lacrimation, itching, scratching, smarting, or burning eyes), nose (blocked, itchy, or running or attacks of sneezing or bleeding), and lower airways (dyspnea, wheezing, chest tightness, or dry cough) during the last 12 months. The symptoms were denoted "work-related" if they appeared in relation to special work tasks or if they improved during weekends or holidays. For the work-related symptoms, about 28% (16) of the workers had symptoms of the nose, 23% (14) had symptoms of the eyes, 12% (4) reported symptoms of the lower airways, and 8% (0) had nose bleeds. In brackets the percentages of the reference group. Exposure levels of HHPA ranged from <1 $\mu g/m^3$ to 94 $\mu g/m^3$, for MHHPA exposure levels ranged from <3 $\mu g/m^3$ to 77 $\mu g/m^3$.

Drexler, Weber et al. (1994) performed a cross sectional study in a company were HHPA (crystalline solids) and methyltetrahydrophthalic anhydride (MTHPA (liquid)) were processed as the starting materials for the housing units of electrical equipment made of epoxy resins. The manufacturing area consists of two large halls connected by a door that is always open. In the area of hall 1 the epoxy resin is mixed and poured into forms. There is no formation of dust. The freshly moulded housing units are then processed further in both halls at a temperature of approximately 80 °C. One hundred and ten members of staff were investigated and their average duration of employment at the factory was 8 years. Approximately 20 % of the workforce declined to take part in the investigation, which was carried out on a voluntary basis. Smarting eyes, rhinitis, rhinoconjunctivitis, dry cough, shortness or breath or asthma at the workplace more than twice a week, with no complaints at the weekends and during holidays, were evaluated as indicating an occupationally induced type I allergy. For workers with the indication of an occupationally induced type I allergy and a positive skin prick test reaction a challenge test was carried out. The challenge simulated the situation of the workplace as closely as possible. The subjects had to handle the materials (HHPA and MTHPA heated to about 80 °C) in a small room for about 10 minutes. Direct inhalation of the substances or of their vapors was avoided. In order to identify unspecific irritation, the physician was present in the testing room during the exposure After the exposure the subjects underwent regular clinical examination and whole-body plethysmography was performed. Among the 109 employees exposed to HHPA and MTHPA (for subject 110 no sera was available), 16 were found to have specific IgE against HHPA conjugates in their sera. With 15 of these persons specific IgE against MTHPA was also detectable which could be indicative for possible cross reactivity. In the collective investigated, a prevalence rate of sensitisation of 15 % can be assumed. In six cases (5 %), this sensitisation was clinically relevant, with all cases diagnosed with rhinitis, two with additional conjunctivitis and two with additional asthma due to working materials.

In a follow-up study fours years later of the same group at the same company the effect of hygiene measures was measured (Drexler, Schaller et al. 1999). Hygiene measures consisted of the epoxy resin being made in a closed system with a modified hardener (MTHPA in a suspension with mineral compounds) and HHPA not being used any more. The other conditions at the workplace have not changed and the amount of epoxy resin produced is almost the same. Overall, 27 people examined in 1991 had left the plant. Fourteen of them replied to a send questionnaire (five of them were recognized as already sensitized in the previous study). Two of them (both sensitized) said that health problems were the reason for leaving the plant, and seven (four sensitized) reported that they have fewer allergic symptoms (rhinitis, cough, shortness of breath) since leaving the plant. Of the six people with clinically relevant sensitisation confirmed by a challenge test in 1991, five were still at their workplace. In 1995, there were fewer work related symptoms in sensitized subjects, who complained of symptoms in 1991. Two people recognized as sensitized in 1991 developed symptoms of rhinitis between 1991 and 1995.

Yokota, Johyama et al. (2002) investigated thirty-two workers in a plant manufacturing light-emitting diodes (LEDs) for portable telephones were studied 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. It was visually demonstrated by smoke tubes 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 physical examination was performed by a physician, and venous blood samples were obtained with informed consent for serologic investigations. Rhinitis, conjunctivitis, or asthma in the workplace more than twice a week, with no complaints at the weekends or during holidays, were evaluated as indicating work-related symptoms. Eight (25%) of the 32 workers tested had positive HHPA specific IgE. Five had work-related rhinitis and three with additional conjunctivitis. None of the subjects had yet had 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.

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 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). Two studies (Nielsen, Welinder et al. 2001; Rosqvist, Nielsen et al. 2003) on the relationship between exposure to HHPA and specific IgE sensitisation provided a basis for deriving a reference value. It concerns two different study populations from the same research group, with combined exposure to MHHPA and HHPA, but with data separated for allergic IgE-mediated sensitisation and exposure levels for both MHHPA and HHPA. 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. 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 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

In the registration dossier, an inhalation long term DNEL of 7.05 mg/m^3 is derived based on the 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. On the contrary, inhalatory exposure estimates of HHPA in the registration dossier (see Annex I, table A.3; confidential data) indicate a realistic risk for sensitisation.

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 summarized the available epidemiological data as follows:

Table 4.2: Critical effects in humans with corresponding exposure levels of cyclic acid anhydrides (adapted 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 indicates that HHPA is among the more potent cyclic acid anhydrides in the group of cyclic acid anhydrides.

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

HHPA is covered by index number 607-102-00-X of Regulation (EC) No 1272/2008[4] 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

[4] 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.

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 describes several cases of occupational asthma due to exposure to HHPA indicating the clear potential of HHPA 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 HHPA 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 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 HHPA, a respiratory sensitiser, serious and permanent organ dysfunction is a possible outcome. HHPA 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, 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 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 HHPA exposure. Acute high exposures may lead to the reactive airways dysfunction syndrome.

[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.

The case reports and epidemiology studies in worker populations have shown that health effects such as rhinitis, conjunctivitis and occupational asthma can result from HHPA 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.

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 HHPA 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 HHPA 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. MHHPA, 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 (Sastre et al. 2003) 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 HHPA 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 HHPA 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 HHPA 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

In the registration dossier, an inhalation long term DNEL of 7.05 mg/m^3 is derived based on the 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. On the contrary, inhalatory exposure estimates of HHPA in the registration dossier indicate a realistic risk for sensitisation.

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 sensitized person may still be able to lead a relatively 'normal' life away from the workplace however this 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 HHPA, permanent impairment of lung function due to HHPA 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 ample data on the sensitizing properties of HHPA 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 exposures to HHPA 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 HHPA 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 HHPA and CMR substances.

	Carcinogenic & mutagenic	**Reproductive – development**	**Hexahydrophthalic anhydride (HHPA)**
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. HHPA 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, no validated animal model is available for the determination of respiratory sensitisation. From the human clinical data of HHPA induces occupational asthma, it is not possible to derive a "safe" no effect level for sensitisation. Every level of exposure to HHPA 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:

HHPA is covered by index number 607-102-00-X in Annex VI, part 3 of Regulation (EC) No 1272/2008[6] and classified as respiratory sensitiser, amongst other.

There is scientific evidence that HHPA 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 HHPA may result in persistent symptoms of respiratory hyper-sensitivity after prolonged exposure. Respiratory diseases including occupational asthma after exposure to HHPA have been recorded in several studies, confirming that HHPA can cause serious and permanent impairment of lung function.

Equivalent concern:

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

- A cross-sectional study of twenty-seven workers carried out in a plant manufacturing bushings for electrical transformers showed that:
    - Four workers (15%) reported occupational asthma, two also reported nocturnal cough, shortness of breath, or wheezing.
    - All four asthmatic workers also developed occupationally related rhinitis and conjunctivitis.
    - Eighteen of the remaining 23 workers reported nasal and/or ocular symptoms while they were at work.
    - Exposure levels ranged from 1.9 mg/m^3 (range 600–3100 µg/m^3) to 3.8 mg/m^3 (range 1.3–8.2 mg/m^3). Three of the workers with occupational asthma worked in the lower exposure area, the other one in both the higher and lower exposure area.
- A study was performed in a plant producing capacitors, fixed and isolated with epoxy resin with HHPA and MHHPA as hardeners:
    - 154 workers exposed to HHPA and MHHPA were examined. As a reference group 57 subjects were recruited with no heavy exposure to sensitizing or irritating agents.
    - For the work-related symptoms, ~ 28% of the workers had symptoms of the nose (blocked, itchy, or running or attacks of sneezing or bleeding),
    - 23% had symptoms of the eyes (lacrimation, itching, scratching, smarting, or burning eyes),
    - 12% reported symptoms of the lower airways (dyspnea, wheezing, chest tightness,

[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.

or dry cough), and 8% had nose bleeds.

- Exposure levels of HHPA ranged from <1 µg/m^3 to 94 µg/m^3, for MHHPA exposure levels ranged from <3 µg/m^3 to 77 µg/m^3.

- Thirty-two workers were investigated in a plant manufacturing light-emitting diodes (LEDs), using both HHPA and MHHPA.
  - Eight (25%) of the 32 workers tested had positive HHPA specific IgE.
  - Five had work-related rhinitis and three with additional conjunctivitis.
  - 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.
- A total of 31 sensitized and non-sensitized workers exposed to HHPA were included in a case control study.
  - Twenty of the subjects (65%) complained of work-related nasal symptoms, of those twenty subjects, eleven workers were sensitized against HHPA.
  - Eleven workers (35%) were not sensitized and displayed no work-related symptoms.
- A prospective cohort study was performed in 66 individuals (follow up time between 1 and 7 years) hired at a facility requiring HHPA for its manufacture. At their date of hire, none of the study population had previous exposure to acid anhydrides, and none had antibody against HHPA conjugated to human serum albumin (HHPA-HSA).
  - Three newly hired individuals developed occupational asthma due to HHPA exposure.
  - The three employees who developed occupational asthma had worn respirators ever since they started their employment.
  - Exposure measurements had been taken in the breathing zone of worker, however the level of exposure was uncertain.
- In two follow-up studies, workers previously diagnosed with occupational allergic rhinitis, asthma, haemorrhagic rhinitis or a combination thereof due to HHPA exposure were examined one year later. In the meantime they were all removed from exposure. In total 44 workers were followed of which:
  - nine had asthma alone,
  - ten had haemorrhagic rhinitis alone,
  - four had both,
  - 13 had allergic rhinitis alone,
  - four had both asthma and allergic rhinitis,

- four had haemorrhagic rhinitis and allergic rhinitis and
- after removal from exposure (one year), all lung function tests were normal in all workers indicating no permanent damage, however one subject experienced symptoms for more than one year after being exposed. Permanent disability from asthma was reported to be probably related to more than two years of exposure where abnormal pulmonary functions at the time exposure ended was observed in the individuals.

The studies show that HHPA 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 4.2) indicates that HHPA 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 HHPA 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 HHPA 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 HHPA, cis-HHPA and trans-HHPA 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 humans 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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