AGREEMENT OF THE MEMBER STATE COMMITTEE

ON THE IDENTIFICATION OF
CYCLOHEXANE-1,2-DICARBOXYLIC ANHYDRIDE,
CIS-CYCLOHEXANE-1,2-DICARBOXYLIC ANHYDRIDE,
TRANS-CYCLOHEXANE-1,2-DICARBOXYLIC ANHYDRIDE

AS SUBSTANCES OF VERY HIGH CONCERN

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

Adopted on 13 December 2012

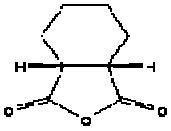
This agreement concerns

Substance name:	**EC number:**	**CAS number:**
cyclohexane-1,2-dicarboxylic anhydride (HHPA) [1]	**201-604-9**	**85-42-7**
cis-cyclohexane-1,2-dicarboxylic anhydride (cis-HHPA) [2]	**236-086-3**	**13149-00-3**
trans-cyclohexane-1,2-dicarboxylic anhydride (trans-HHPA) [3]	**238-009-9**	**14166-21-3**

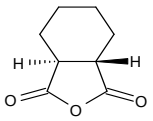
The individual cis- [2] and trans- [3] isomer substances and all possible combinations of the cis- and trans-isomers [1] are covered by this agreement.

Molecular formula: $C_8H_{10}O_3$

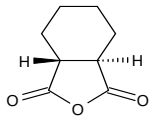
Structural formulas:



***cis*-HHPA**



and



***trans*-HHPA**

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

The Netherlands presented a proposal in accordance with Article 59(3) and Annex XV of the REACH Regulation (28 August 2012, submission number CW009943-17) on identification of *cyclohexane-1,2-dicarboxylic anhydride, cis-cyclohexane-1,2-dicarboxylic anhydride, trans-cyclohexane-1,2-dicarboxylic anhydride* as substances of very high concern due to their respiratory sensitising properties.

The following public name was used throughout the Annex XV dossier: HHPA (deriving from the name hexahydrophthalic anhydride) and covered 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, i.e. cyclohexane-1,2-dicarboxylic anhydride [1].

The Annex XV dossier was circulated to Member States on 3 September 2012 and the Annex XV report was made available to interested parties on the ECHA website on the same day according to Articles 59(3) and 59(4).

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

The dossier was referred to the Member State Committee on 19 November 2012 and was discussed in the meeting on 10-13 December 2012 of the Member State Committee.

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

***Cyclohexane-1,2-dicarboxylic anhydride [1], cis-cyclohexane-1,2-dicarboxylic anhydride [2], trans-cyclohexane-1,2-dicarboxylic anhydride [3]*[2] are identified as substances meeting the criteria of Article 57 (f) of REACH because they are substances with respiratory sensitising properties for which there is scientific evidence of probable serious effects to human health which give rise to an equivalent level of concern to those for other substances listed in paragraphs (a) to (e) of Article 57 of REACH.**

[2] The individual cis- [2] and trans- [3] isomer substances and all possible combinations of the cis- and trans-isomers [1] are covered by this agreement

UNDERLYING ARGUMENTATION
FOR IDENTIFICATION OF SUBSTANCES OF VERY HIGH CONCERN

The following public name is used throughout this section: 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, i.e. cyclohexane-1,2-dicarboxylic anhydride [1].

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[3] 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.
    - 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

[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.

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 $\mu g/m^3$ to 94 $\mu g/m^3$, for MHHPA exposure levels ranged from <3 $\mu g/m^3$ to 77 $\mu g/m^3$.

- 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 $\mu g/m^3$ for HHPA and 2.0 – 52.8 $\mu g/m^3$ 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 in reference 1. Support document for HHPA, MSC 13 December 2012) 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.

Reference:

1. Support Document *cyclohexane-1,2-dicarboxylic anhydride, cis-cyclohexane-1,2-dicarboxylic anhydride, trans-cyclohexane-1,2-dicarboxylic anhydride* (Member State Committee, 13 December 2012)