

AGREEMENT OF THE MEMBER STATE COMMITTEE

**ON THE IDENTIFICATION OF
HEXAHYDROMETHYLPHTHALIC ANHYDRIDE,
HEXAHYDRO-4-METHYLPHTHALIC ANHYDRIDE,
HEXAHYDRO-1-METHYLPHTHALIC ANHYDRIDE,
HEXAHYDRO-3-METHYLPHTHALIC ANHYDRIDE**

AS SUBSTANCES OF VERY HIGH CONCERN

**According to Articles 57 and 59 of
Regulation (EC) 1907/2006¹**

Adopted on 13 December 2012

This agreement concerns

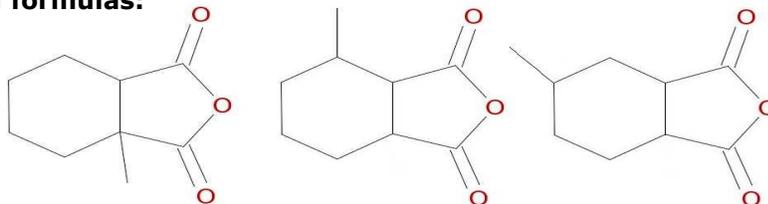
Substance name:	EC number:	CAS number:
Hexahydromethylphthalic anhydride (MHHPA) [1]	247-094-1	25550-51-0
Hexahydro-4-methylphthalic anhydride [2]	243-072-0	19438-60-9
Hexahydro-1-methylphthalic anhydride [3]	256-356-4	48122-14-1
Hexahydro-3-methylphthalic anhydride [4]	260-566-1	57110-29-9

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 by this agreement.

Molecular formula:

C₉H₁₂O₃

Structural formulas:



¹Regulation (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 CW010807-22) on identification of *Hexahydromethylphthalic anhydride*, *Hexahydro-4-methylphthalic anhydride*, *Hexahydro-1-methylphthalic anhydride*, *Hexahydro-3-methylphthalic anhydride* as substances of very high concern due to their respiratory sensitising properties.

The following public name was used throughout the dossier: MHHPA (deriving from the name methylhexahydrophthalic anhydride) and covered 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 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):

***Hexahydromethylphthalic anhydride [1], Hexahydro-4-methylphthalic anhydride [2], Hexahydro-1-methylphthalic anhydride [3], Hexahydro-3-methylphthalic anhydride [4]*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 isomers [2], [3] and [4] (including their cis- and trans- stereo isomeric forms) and all possible combinations of the 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: 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).

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 1272/2008³ 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
 - 16% responded positive to IgG.
 - The exposures in 3 plants ranged from <1 to 189 $\mu\text{g}/\text{m}^3$ for the substances combined. The highest mean exposure to MHHPA was 12 $\mu\text{g}/\text{m}^3$.
- 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

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.

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 $\mu\text{g}/\text{m}^3$ for HHPA and from <3 to 77 $\mu\text{g}/\text{m}^3$ for MHPA.
 - 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 MHPA 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 $\mu\text{g}/\text{m}^3$ for HHPA and 2.0 – 52.8 $\mu\text{g}/\text{m}^3$ for MHPA.

The studies show that MHPA is causing respiratory health effects already at relatively low exposure levels (10-50 $\mu\text{g}/\text{m}^3$). 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 MHPA, MSC 13 December 2012) indicates that MHPA 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 MHPA 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 MHPA 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.

Reference:

1. Support Document *Hexahydromethylphthalic anhydride, Hexahydro-4-methylphthalic anhydride, Hexahydro-1-methylphthalic anhydride, Hexahydro-3-methylphthalic anhydride* (Member State Committee, 13 December 2012)