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# Executive summary

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## Scope

At request of the Minister of Social Affairs and Employment, the Dutch expert Committee on Occupational Exposure Safety (DECOS), one of the permanent committees of experts of the Health Council, proposes health-based recommended occupational exposure limits for chemical substances in the air in the workplace. These recommendations serve as basis in setting legally binding occupational exposure limits by the minister. In this advisory report, the committee evaluates the consequences of exposure to cyclic acid anhydrides\*, and derives a health-based recommended occupational exposure limit (HBR-OEL).

In a first step the toxicity of the compounds was evaluated. This is done in cooperation with the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. The results of the evaluation, which are published in 2004, are included in Part II of this advisory report. In the first part, the DECOS describes the most relevant data, supplied by newly presented data, and advices on an HBR-OEL. The conclusions of the DECOS are based on scientific papers published before December 2009.

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\* Cyclic acid anhydrides evaluated in this report: chlorendic anhydride (CA); dodecenylsuccinic anhydride (DSA); himic anhydride (HA); maleic anhydride (MA); hexahydrophthalic anhydride (HHPA); methyl hexahydrophthalic anhydride (MHHPA); methyl tetrahydrophthalic anhydride (MTHPA); phthalic anhydride (PA); pyromellitic dianhydride (PMDA); succinic anhydride (SA); tetrabromophthalic anhydride (TBPA); tetrachlorophthalic anhydride (TCPA); tetrahydrophthalic anhydride (THPA); trimellitic anhydride (TMA).

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## Physical and chemical properties

Cyclic acid anhydrides are mainly powders or crystals; methyl derivatives of the cyclic acid anhydrides are oily liquids. Most cyclic acid anhydrides dissolve in organic solvents, such as in alcohol and benzene. With alcohol they are quickly hydrolyzed by water to form carboxylic acids. At least phthalic and maleic anhydride also dissolve in water.

Cyclic acid anhydrides are broadly used in the chemical industry, in particular in the production of polyesters, plastics and resins. They do not occur naturally, but may be found as contaminants in the environment.

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## Monitoring

In general, samples of cyclic acid anhydrides in the air are taken by the use of special absorption tubes, Teflon or PVF filters, or a combination of these possibilities. Various analysis methods are suitable to determine the concentration of acid anhydrides in the samples. These include gas chromatography combined with flame ionisation detection, mass spectrometric detection, and electron capture detection methods.

Analysis methods are available for analyzing in urine the dicarboxylic acids formed from the corresponding cyclic acid anhydrides, and for measuring in plasma the dicarboxylic acids formed from HHPA and MHPA.

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## Current limit values

In the Netherlands, no legally binding standards exist for cyclic acid anhydrides. Elsewhere, for some acid anhydrides occupational exposure limits are set. These vary between 200 and 12,000  $\mu\text{g}/\text{m}^3$  for phthalic anhydride, 40  $\mu\text{g}/\text{m}^3$  for trimellitic anhydride, and between 400 to 1,200  $\mu\text{g}/\text{m}^3$  for maleic anhydride, and include eight-hour and 15-minute time weighted average concentrations, and ceiling values.

PA, TMA, MA, HHPA, MHPA, MTHPA, THPA, TCPA, HA, and PMDA are classified by the European Union as sensitizers by inhalation and skin contact (R42 and R42).

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## Kinetics

Investigations in humans reveal that hexahydrophthalic anhydride is efficiently taken up by the body after inhalation, whereas uptake via the skin is minimal. Regarding other cyclic acid anhydrides, no data on uptake after inhalation, or via other routes of exposure is known.

In blood, cyclic acid anhydrides bind to hemoglobin, which is present in red blood cells, and to proteins in plasma, such as albumin. They likely bind also to proteins in organs, such as those of the respiratory and gastrointestinal tract, and the kidneys.

Approximately 85% of the inhaled hexahydrophthalic anhydride is released from the body via the urine in the form of dicarboxy acids. The half-life, *i.e.*, the time the body needs to half the dose of dicarboxy acids in plasma, depends on the type of acid anhydride, and varies from two to fourteen hours.

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## Mechanism of toxicity

The most marked adverse health effects due to exposure to cyclic acid anhydrides are irritation and allergic hypersensitivity. Irritation may be caused by both cyclic acid anhydrides and their hydrolysis products.

Allergic hypersensitivity by cyclic acid anhydrides is caused by induction of an IgE mediated specific immune response (immediate type). This is known because in both humans and animals specific antibodies of the IgE type are found in the blood. These antibodies are involved in allergic processes, and the presence of them points to allergic sensitisation. Sensitisation is a crucial and necessary step in the development of allergies. Continuing exposure after being sensitised may lead to disorders, such as contact urticaria, allergic rhinitis and rhinoconjunctivitis, and allergic asthma.

There are indications that cyclic acid anhydrides might also induce other types of immune responses, involving induction of specific IgG antibodies, and delayed-type of responsiveness.

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## Effects

### Observations in humans

Skin contact may lead to contact urticaria.

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Short-term inhalation may lead to acute effects, such as inflammation of the mucous membranes in the upper and lower respiratory tract. These types of effects might well be caused by irritation.

Of some cyclic acid anhydrides data are collected on the allergic hypersensitivity and respiratory disorders, due to occupational exposure. However, not in all cases respiratory disorders could be associated with allergic hypersensitivity and thus with allergy. This is caused by the fact that irritation gives comparable symptoms. Furthermore, it is possible that in some cases irritation and allergy appeared at the same time in the same person.

Estimations on the prevalences of occupational asthma due to exposure to cyclic acid anhydrides vary between 8 and 18% for PA, 2 to 12% for TMA, 15% for HHPA, 11% for MHHPA, and 3 to 39% for TCPA.

In principle, for most cyclic acid anhydrides evaluated in this advisory report, cases of allergic sensitisation have been reported due to occupational exposure. However, not for all acid anhydrides this could be clearly correlated with a certain exposure level. For those for which data on exposure levels were available, the lowest levels at which still cases of allergic sensitisation were reported varied from less than 1  $\mu\text{g}/\text{m}^3$  (TMA, HHPA and MHHPA), and 15  $\mu\text{g}/\text{m}^3$  (MTHPA), to exposure levels of hundreds of micrograms per cubic meter (PA and TCPA). In all cases, at these exposure levels also (allergic) respiratory symptoms were reported, such as rhinitis and asthma. Data on lower exposure levels of the respective compounds are not available, except for TMA, thus it is possible that below the lowest measured levels, still allergic sensitisation and symptoms may be induced.

Finally, there are cases reported on hemorrhagic alveolitis and anaemia, and allergic alveolitis and laryngitis. No data are available on adverse effects in other organs than the respiratory tract.

### Observation in animals

A few studies indicate that certain cyclic acid anhydrides can lead to skin and eye irritation by direct contact. There are, however, potency differences among the different acid anhydrides. For instance, phthalic anhydride caused slight irritation in the eyes of rabbits, but maleic and trimellitic anhydride caused moderate to severe eye irritation.

A limited number of animal studies has been performed, using guinea pigs, rats and mice, in which the induction of allergic sensitisation of cyclic acid anhydrides (PA, TMA, HHPA, MHHPA, and MTHPA) was investigated. The majority of the studies had a so-called biphasic design. This means that animals

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underwent two phases of exposure, a sensitisation phase and a challenge phase. Sometimes different exposure routes and exposure levels were chosen for each phase.

Similar adverse health effects were observed in animals as in man. For instance, after dermal and inhalation exposure, specific IgE antibodies were found in blood, an indication of allergic sensitisation. Also pathological changes in lung tissue were observed.

Regarding investigations on inhalation exposure, the lowest concentration at which still elevated levels of TMA-specific IgE was found was 400  $\mu\text{g}/\text{m}^3$ , whereas no elevated levels were found after exposure to 40  $\mu\text{g}/\text{m}^3$ . However, the low number of animals and the short duration of exposure hamper a final conclusion on these outcomes. Concentrations of 30 to 40  $\mu\text{g}/\text{m}^3$  caused histopathological changes in the lungs. In another animal study, increased levels of antibody response were observed at 10  $\mu\text{g TMA}/\text{m}^3$  and higher. Furthermore, the increase in response correlated strongly with an increase in hemorrhagic lung foci and lung weight.

In rats, hamsters, and monkeys, which were exposed to maleic anhydride (1,100 to 9,800  $\mu\text{g}/\text{m}^3$ ) for a half year, no abnormalities were found in the lungs, liver, pancreas, bone marrow, and kidneys. In rodents, however, irritation of the nasal mucous membranes was reported, but this was reversible and could not be correlated to the level of exposure.

Animal data on long-term exposure to other cyclic acid anhydrides is lacking.

There is also a lack of data on possible carcinogenic properties. The few available data on genotoxicity are negative.

Furthermore, no indications for effects on reproduction and progeny have been found. However, hardly any data on reproductive toxicity is available.

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## **Procedure by assessing health-based occupational exposure limits for allergens**

### The choice of critical effect

DECOS considers the induction of allergic sensitisation as the critical adverse health effect against which workers should be protected. The main reason being that allergic sensitisation is an irreversible change, that is associated with a higher risk in developing allergic reactions. By preventing allergic sensitisation, DECOS expects that also the development of an allergy due to continued exposure will be prevented. Furthermore, it expects that by preventing sensitisation also induction of irritation of the respiratory tract will be prevented.

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The committee prefers the use of data on anhydride-specific IgE mediated sensitisation, because according to the current scientific views, specific IgG mediated sensitisation is less associated with allergic symptoms.

### Choice of HBR-OELs or reference values

In the scientific literature it is discussed whether for allergens a threshold level exists, below which no cases of allergic sensitisation or allergy symptoms are to be expected.

Based on the current knowledge, the Health Council concluded in its recently published advisory report that based on current knowledge, in theory a threshold level exists for allergic sensitisation by inhaled allergens. This implies that a health-based recommended occupational exposure limit can be calculated, using the same procedures and methods as those for other non-carcinogenic substances.

However, in the same report, the Health Council emphasizes that for most allergens, in practice it will not be possible to calculate a reliable health-based recommended occupational exposure limit. The reason being that, in most cases, the threshold level will be too low to discern using the techniques presently available.

For those allergens, the Health Council proposed an alternative approach, involving determination of reference values, *i.e.* concentration levels that correspond to predefined accepted levels of risk of allergic sensitisation.

The procedure outlined is followed by DECOS to derive advisory values for cyclic acid anhydrides. For this purpose epidemiological data served as basis. Furthermore, for the recommendations, DECOS used the benchmark dose software of the US Environmental Protection Agency to assess the best fitting shape of the exposure-response relationship. The relationship was then used to derive an exposure level that could serve as point of departure in estimating reference values.

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### Evaluation and recommendations

The outcomes and considerations of the individual cyclic acid anhydrides are given below.

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## TMA

Exposure and response data were available from an observational study with a cohort design (Grammer *et al.* (1999)). From the fitted dose response curve, an exposure level was calculated at which 10% of the occupationally exposed population will get specifically sensitized to TMA. This levels corresponded to 18  $\mu\text{g TMA}/\text{m}^3$ . This level was used as a starting point for calculating exposure levels with lower sensitizing risks, *i.e.* 0.1% and 1%.

Using a linear extrapolation model, the exposure levels (reference values) corresponding to an additional risk of 0.1% and 1% amount to:

- 0.18  $\mu\text{g TMA}/\text{m}^3$ , which corresponds to an additional risk of 0.1% due to occupational exposure, as an 8-hour time weighted average concentration
- 1.8  $\mu\text{g TMA}/\text{m}^3$ , 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 sensitised to TMA in the general population. Furthermore, the reference values serve as examples, since also policy and social considerations should be taken into account in deciding on the level of the predefined additional risk levels. In the Netherlands, no decisions have yet been made about accepted additional response levels for allergic sensitisation of inhaled allergens.

## HHPA

Exposure and response data were available from an observational study (Rosqvist *et al.* (2003)). From the fitted dose response curve, an exposure level was calculated at which 10% of the occupationally exposed population will get specifically sensitized to HHPA. This levels corresponded to 0.73  $\mu\text{g HHPA}/\text{m}^3$ . This level was used as a starting point for calculating exposure levels with lower sensitizing risks, *i.e.* 0.1% and 1%.

Using a linear extrapolation model, the exposure levels (reference values) corresponding to an additional risk of 0.1% and 1% amount to:

- 0.007  $\mu\text{g HHPA}/\text{m}^3$ , which corresponds to an additional risk of 0.1% due to occupational exposure, as an 8-hour time weighted average concentration
  - 0.07  $\mu\text{g HHPA}/\text{m}^3$ , which corresponds to an additional risk of 1% due to occupational exposure, as an 8-hour time weighted average concentration.
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The predefined additional risks are extra risks caused by occupational exposure that comes on top of the risk of getting sensitised to HHPA in the general population. Furthermore, the reference values serve as examples, since also policy and social considerations should be taken into account in deciding on the level of the predefined additional risk levels. In the Netherlands, no decisions have yet been made about accepted additional response levels for allergic sensitisation of inhaled allergens

CA, DSA, HA, MA, MHHPA, MTHPA, PA, PMDA, SA, TBPA, TCPA, THPA

The DECOS abstains from making recommendations for the following cyclic acid anhydrides, because of a lack of adequate data on allergic sensitisation and respiratory symptoms to derive an HBR-OEL of reference values:

- chlorendic anhydride (CA)
- dodecenylsuccinic anhydride (DSA)
- himic anhydride (HA)
- maleic anhydride (MA)
- methyl hexahydrophthalic anhydride (MHHPA)
- methyl tetrahydrophthalic anhydride (MTHPA)
- phthalic anhydride (PA)
- pyromellitic dianhydride (PMDA)
- succinic anhydride (SA)
- tetrabromophthalic anhydride (TBPA)
- tetrachlorophthalic anhydride (TCPA)
- tetrahydrophthalic anhydride (THPA).

As an additional consideration, the DECOS notes that it would be prudent to avoid respiratory exposure to these cyclic acid anhydrides in as much as possible, in particular in those conditions where exposure exceeds concentrations in which better studied anhydrides, such as TMA and HHPA, are known to cause sensitization.