Concise International Chemical Assessment Document 75

CYCLIC ACID ANHYDRIDES: HUMAN HEALTH ASPECTS

First draft prepared by Dr James H. Kim, Dr Herman J. Gibb, and Ms Annette Iannucci, Sciences International, Inc., Alexandria, VA, USA

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The **International Programme on Chemical Safety (IPCS)**, established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organization (ILO), and the World Health Organization (WHO). The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

The **Inter-Organization Programme for the Sound Management of Chemicals (IOMC)** was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, the United Nations Institute for Training and Research, and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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FOREWORD

Concise International Chemical Assessment Documents (CICADs) are published by the International Programme on Chemical Safety (IPCS)—a cooperative programme of the World Health Organization (WHO), the International Labour Organization (ILO), and the United Nations Environment Programme (UNEP). CICADs have been developed from the Environmental Health Criteria documents (EHCs), more than 200 of which have been published since 1976 as authoritative documents on the risk assessment of chemicals.

International Chemical Safety Cards on the relevant chemical(s) are attached at the end of the CICAD, to provide the reader with concise information on the protection of human health and on emergency action. They are produced in a separate peer-reviewed procedure at IPCS. They may be complemented by information from IPCS Poison Information Monographs (PIM), similarly produced separately from the CICAD process.

CICADs are concise documents that provide summaries of the relevant scientific information concerning the potential effects of chemicals upon human health and/or the environment. They are usually based on selected national or regional evaluation documents or on existing EHCs. Before acceptance for publication as CICADs by IPCS, these documents undergo extensive peer review by internationally selected experts to ensure their completeness, accuracy in the way in which the original data are represented, and the validity of the conclusions drawn.

The primary objective of CICADs is characterization of hazard and dose–response from exposure to a chemical. CICADs are not a summary of all available data on a particular chemical; rather, they include only that information considered critical for characterization of the risk posed by the chemical. The critical studies are, however, presented in sufficient detail to support the conclusions drawn. For additional information, the reader should consult the identified source documents upon which the CICAD has been based.

Risks to human health and the environment will vary considerably depending upon the type and extent of exposure. Responsible authorities are strongly encouraged to characterize risk on the basis of locally measured or predicted exposure scenarios. To assist the reader, examples of exposure estimation and risk characterization are provided in CICADs, whenever possible. These examples cannot be considered as representing all possible exposure situations, but are provided as guidance only. The reader is referred to EHC 170.[1]

While every effort is made to ensure that CICADs represent the current status of knowledge, new information is being developed constantly. Unless otherwise stated, CICADs are based on a search of the scientific literature to the date shown in the executive summary. In the event that a reader becomes aware of new information that would change the conclusions drawn in a CICAD, the reader is requested to contact IPCS to inform it of the new information.

Procedures

The flow chart on page 2 shows the procedures followed to produce a CICAD. These procedures are designed to take advantage of the expertise that exists around the world—expertise that is required to produce the high-quality evaluations of toxicological, exposure, and other data that are necessary for assessing risks to human health and/or the environment. The IPCS Risk Assessment Steering Group advises the Coordinator, IPCS, on the selection of chemicals for an IPCS risk assessment based on the following criteria:

- there is the probability of exposure; and/or
- there is significant toxicity/ecotoxicity.

Thus, it is typical of a priority chemical that:

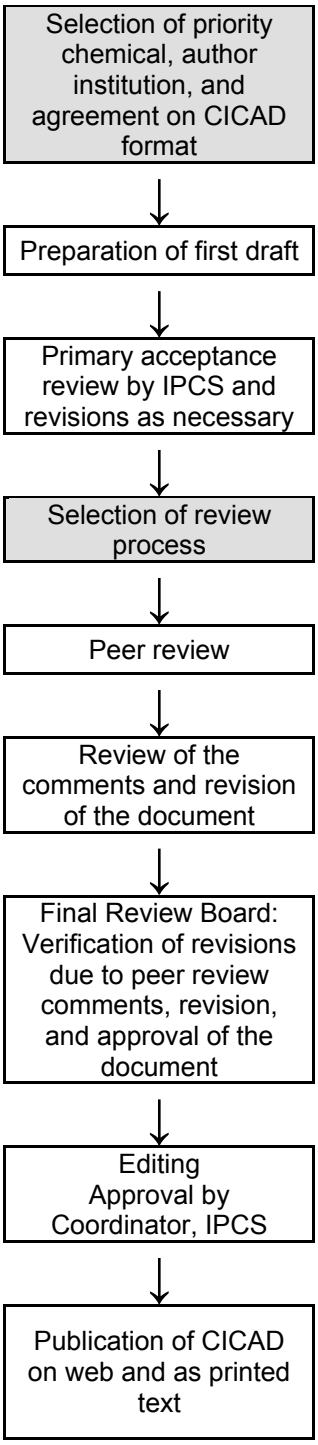
- it is of transboundary concern;
- it is of concern to a range of countries (developed, developing, and those with economies in transition) for possible risk management;
- there is significant international trade;
- it has high production volume;
- it has dispersive use.

The Steering Group will also advise IPCS on the appropriate form of the document (i.e. a standard CICAD or a de novo CICAD) and which institution bears the responsibility of the document production, as well as on the type and extent of the international peer review.

The first draft is usually based on an existing national, regional, or international review. When no appropriate source document is available, a CICAD may be produced de novo. Authors of the first draft are usually, but not necessarily, from the institution that developed the original review. A standard outline has been developed to encourage consistency in form. The

[1] International Programme on Chemical Safety (1994) *Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits.* Geneva, World Health Organization (Environmental Health Criteria 170) (also available at http://www.who.int/pcs/).

CICAD PREPARATION FLOW CHART



Advice from Risk Assessment Steering Group

Criteria of priority:

- there is the probability of exposure; and/or
- there is significant toxicity/ecotoxicity.

Thus, it is typical of a priority chemical that:

- it is of transboundary concern;
- it is of concern to a range of countries (developed, developing, and those with economies in transition) for possible risk management;
- there is significant international trade;
- the production volume is high;
- the use is dispersive.

Special emphasis is placed on avoiding duplication of effort by WHO and other international organizations.

A usual prerequisite of the production of a CICAD is the availability of a recent high-quality national/regional risk assessment document = source document. The source document and the CICAD may be produced in parallel. If the source document does not contain an environmental section, this may be produced de novo, provided it is not controversial. If no source document is available, IPCS may produce a de novo risk assessment document if the cost is justified.

Depending on the complexity and extent of controversy of the issues involved, the steering group may advise on different levels of peer review:

- standard IPCS Contact Points;
- above + specialized experts;
- above + consultative group.

first draft undergoes primary review by IPCS to ensure that it meets the specified criteria for CICADs.

The second stage involves international peer review by scientists known for their particular expertise and by scientists selected from an international roster compiled by IPCS through recommendations from IPCS national Contact Points and from IPCS Participating Institutions. Adequate time is allowed for the selected experts to undertake a thorough review. Authors are required to take reviewers' comments into account and revise their draft, if necessary. The resulting second draft is submitted to a Final Review Board together with the reviewers' comments. At any stage in the international review process, a consultative group may be necessary to address specific areas of the science. When a CICAD is prepared de novo, a consultative group is normally convened.

The CICAD Final Review Board has several important functions:

- to ensure that each CICAD has been subjected to an appropriate and thorough peer review;
- to verify that the peer reviewers' comments have been addressed appropriately;
- to provide guidance to those responsible for the preparation of CICADs on how to resolve any remaining issues if, in the opinion of the Board, the author has not adequately addressed all comments of the reviewers; and
- to approve CICADs as international assessments.

Board members serve in their personal capacity, not as representatives of any organization, government, or industry. They are selected because of their expertise in human and environmental toxicology or because of their experience in the regulation of chemicals. Boards are chosen according to the range of expertise required for a meeting and the need for balanced geographic representation.

Board members, authors, reviewers, consultants, and advisers who participate in the preparation of a CICAD are required to declare any real or potential conflict of interest in relation to the subjects under discussion at any stage of the process. Representatives of nongovernmental organizations may be invited to observe the proceedings of the Final Review Board. Observers may participate in Board discussions only at the invitation of the Chairperson, and they may not participate in the final decision-making process.

1. EXECUTIVE SUMMARY

This Concise International Chemical Assessment Document (CICAD)[1] on cyclic acid anhydrides was prepared by Sciences International, Inc. and is based on a review prepared by the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals and the Dutch Expert Committee on Occupational Standards (Keskinen, 2004). To address literature citations not included in this review, a comprehensive literature search of several online databases was conducted in June 2006. Information on the source document and its peer review is presented in Appendix 2. Information on the peer review of this CICAD is presented in Appendix 3. This CICAD was considered and approved as an international assessment at a Final Review Board meeting held in Helsinki, Finland, on 26–29 March 2007. Participants at the Final Review Board meeting are presented in Appendix 4. International Chemical Safety Cards for several cyclic acid anhydrides, produced by the International Programme on Chemical Safety (IPCS), are reproduced in this CICAD (IPCS, 2000a,b,c,d, 2005a,b,c,d,e, 2006).

Cyclic acid anhydrides are widely used in the chemical industry. Acid anhydrides are irritants and are especially potent sensitizing agents. This document deals with the following anhydrides of concern: phthalic anhydride, trimellitic anhydride, maleic anhydride, hexahydrophthalic anhydride, methyl hexahydrophthalic anhydride, methyl tetrahydrophthalic anhydride, tetrahydrophthalic anhydride, tetrachlorophthalic anhydride, pyromellitic dianhydride, himic anhydride, succinic anhydride, dodecenylsuccinic anhydride, chlorendic anhydride, and tetrabromophthalic anhydride.

Solid sorbent tubes, bubblers, and impingers are used for the collection of samples of cyclic acid anhydride vapours. Bubblers and impingers sample the anhydride as the corresponding acid. The impinger or bubbler method and polyvinyl chloride (PVC) or Teflon filters in series with solid sorbent tubes are used to sample particles. To recover both particles and vapours, sampling with both methods is recommended in studies where the state of exposure is unknown. Gas chromatography (GC) with flame ionization detection (FID), electron capture detection (ECD), or mass spectrometric (MS) detection have been used for analysis of samples.

Following esterification, dicarboxylic acids of various anhydrides in urine have been analysed using GC-ECD and GC-MS. A method has also been developed for the analysis of anhydrides in plasma.

The cyclic acid anhydrides are used mainly in the manufacture of polyester and alkyd resins and plasticizers and as epoxy resin hardeners. Cyclic acid anhydrides are mainly powders or crystals.

Information on the environmental transport, distribution, and transformation of cyclic acid anhydrides is unavailable. Based on its chemical properties, phthalic anhydride is expected to undergo rapid hydrolysis to phthalic acid in aqueous environments and moist soil. Based on its low vapour pressure, phthalic anhydride will not undergo significant volatilization from water or soil. In the air, phthalic anhydride will react with hydroxyl radicals.

Cyclic acid anhydrides are primarily absorbed by inhalation, although dermal absorption has also been reported. Studies of cyclic acid anhydride inhalation in humans have demonstrated excretion of the corresponding dicarboxylic acid in the urine. Animal studies that evaluated the tissue distribution of cyclic acid anhydrides have found that the mucosa of the nasal region and trachea contained the highest levels of the chemicals.

The anhydride moiety readily reacts with amino acids, forming protein conjugates such as serum albumin conjugates. Occupationally exposed workers possess measurable plasma protein and albumin adduct levels that correlate with exposure. Protein chemistry experiments have demonstrated that the major amino acid bound by cyclic acid anhydrides is lysine.

The half-time of cyclic acid anhydrides in urine of humans varies from 2–3 h for hexahydrophthalic acid to 14 h for phthalic acid. Plasma half-times have been reported to be 1.7–1.8 h for hexahydrophthalic acid.

Acute toxicity data in animals in the form of median lethal doses (LD_{50} values) ranged from 75.5 mg/kg body weight (bw) to >15 800 mg/kg bw by oral, inhalation, dermal, or intraperitoneal routes of administration. Phthalic anhydride and maleic anhydride have the lowest oral LD_{50} values. Animal experiments have demonstrated that maleic anhydride and trimellitic anhydride are extremely strong eye irritants.

Medium-term exposure in animals resulted in nasal tissue irritation in the form of hyperplasia and metaplasia. These inflammatory changes in nasal tissue have been determined to be reversible effects.

Long-term exposure or carcinogenicity studies of the cyclic acid anhydrides in animals are scarce. Long-term feeding studies of phthalic anhydride in rodents provided no evidence of carcinogenicity. In a limited study of rats injected subcutaneously with succinic

[1] For a complete list of acronyms and abbreviations used in this report, the reader should refer to Appendix 1.

anhydride, subcutaneous sarcomas at the site of injection were observed.

The mutagenicity and genotoxicity database for cyclic acid anhydrides is limited. Ames *Salmonella typhimurium* and chromosomal aberration assays did not demonstrate mutagenicity or genotoxicity for several cyclic acid anhydrides.

The database for reproductive and developmental toxicity is poor. Reproductive and developmental toxicity was not observed when maleic anhydride was administered to pregnant animals during gestation. One developmental study of phthalic anhydride and succinic anhydride did find malformations in mice exposed during gestation, but only at doses that were maternally toxic. However, this study was conducted using intraperitoneal application of the test compounds, a route of exposure that is of questionable significance to humans.

Many animal studies have evaluated sensitization effects to characterize the immune response patterns and parameters and elucidate the mode of action of these chemicals. Several studies have concluded that cyclic acid anhydrides do not cause allergic contact dermatitis in rodents. Sensitization studies are typically conducted by sensitizing animals to a cyclic acid anhydride and challenging the animals with a conjugate of serum albumin and the anhydride. Specifically, immune responses have been evaluated after challenge by assessing antibody levels and haemorrhagic lung foci. Significant dose–response relationships have been observed between immune responses and exposure to cyclic acid anhydrides. Antibodies that are usually increased after sensitization and challenge are immunoglobulin E (IgE) and IgG, which are reactive towards the anhydride–albumin conjugate that is being studied. An increased number of haemorrhagic lung foci and bronchial hyperreactivity have been observed in rats sensitized and challenged with trimellitic anhydride.

Another approach to studying the sensitization effects of cyclic acid anhydrides is to inhibit specific arms of the immune system and immune response to determine if sensitization is also inhibited. Experiments using cobra venom to inhibit complement activation had no effect on immediate bronchoconstriction or microvascular leakage, although inflammatory cell infiltration was inhibited during trimellitic anhydride–induced asthma. Clodronate-induced depletion of alveolar macrophages in the lung has been demonstrated to alleviate cyclic acid anhydride–induced decreases in lung function, but augments tissue damage and inflammation 24 h after challenge.

Mode of action studies in humans have found that cyclic acid anhydrides cause IgE-mediated urticaria and allergic asthma. Allergic asthma is frequently preceded by IgE-mediated rhinoconjunctivitis. Animal studies have demonstrated that histamine and thromboxane A_2 are responsible for the early and late bronchoconstriction responses to trimellitic anhydride. Leukotrienes and histamine were found to mediate airway exudation. Different immunosuppressant treatments have resulted in inhibition of increased airway responsiveness, lung lesions, and antibody responses to cyclic acid anhydrides.

In humans, cyclic acid anhydrides can cause irritation and sensitization after direct contact with the skin and the mucous membranes or after exposure by inhalation. Irritation is caused by the corresponding dicarboxylic acid that is formed when cyclic acid anhydrides interact with water. The most common allergic diseases are rhinoconjunctivitis and asthma, both immediate-type IgE-mediated allergies.

Because of the sensitizing nature of the cyclic acid anhydrides, tolerable concentrations, as per Environmental Health Criteria 170, cannot be established. As guidance for evaluating the risks of workplace exposure to the various anhydrides, the ranges of concentrations that have caused sensitization and other effects are provided for the various compounds for which data are available. The lowest concentration of any of the cyclic acid anhydrides that has caused effects is 5 $\mu g/m^3$ (methyl tetrahydrophthalic anhydride). By contrast, the lowest concentration of phthalic anhydride that has caused an effect is 1500 $\mu g/m^3$.

2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES

Cyclic acid anhydrides are mainly powders or crystals. Methyl substitution converts them to oily liquids. A halogen—chlorine or bromine—in the molecule endows it with flame retardant capabilities.

Chemical and physical properties of the cyclic acid anhydride compounds discussed in this document are presented in Table 1, and their chemical structures are illustrated in Figure 1. Further details on some of these compounds are provided in the International Chemical Safety Cards reproduced in this document.

Table 1: Physical and chemical properties of selected acid anhydrides.[a]

Acid anhydride	CAS No.	Relative molecular mass	Molecular formula	Melting point (°C)	Solubility
Phthalic anhydride	85-44-9	148.12	$C_8H_4O_3$	130.8	0.62 g/100 ml water; soluble in alcohol and ether
Trimellitic anhydride	552-30-7	192.13	$C_9H_4O_5$	161–163.5	Soluble in acetone, ethyl acetate, and dimethylformamide
Maleic anhydride	108-31-6	98.06	$C_4H_2O_3$	53	40 g/100 ml water; soluble in acetone, ethyl acetate, chloroform, and benzene
Hexahydrophthalic anhydride	85-42-7	154.17	$C_8H_{10}O_3$	Becomes a glassy solid at 35–36	Miscible with benzene, toluene, acetone, carbon tetrachloride, chloroform, ethanol, and ethyl acetate; slightly soluble in petroleum ether
Methyl hexahydrophthalic anhydride	25550-51-0	168.19	$C_9H_{12}O_3$	−29	No information available
Methyl tetrahydrophthalic anhydride$_{44}$[b]	26590-20-5	166.19	$C_9H_{10}O_3$	No information available	No information available
Tetrahydrophthalic anhydride	85-43-8	152.16	$C_8H_8O_3$	101.9	Slightly soluble in petroleum ether and ethyl ether; soluble in benzene
Tetrachlorophthalic anhydride	117-08-8	285.88	$C_8Cl_4O_3$	No information available	No information available
Pyromellitic dianhydride	89-32-7	218.13	$C_{10}H_2O_6$	286	Soluble in some organic solvents; 13.0 mg/100 ml water at 25 °C (estimated)
Himic anhydride	2746-19-2	164.16	$C_9H_8O_3$	No information available	No information available
Succinic anhydride	108-30-5	100.07	$C_4H_4O_3$	119.6	2.4 g/100 ml water at 25 °C; 2.56 g/100 ml ethanol at 25 °C; 0.64 g/100 ml ether at 25 °C; 0.87 g/100 ml chloroform at 25 °C
Dodecenylsuccinic anhydride	25377-73-5	281.44	$C_{16}H_{26}O_3$	No information available	No information available
Chlorendic anhydride	115-27-5	370.84	$C_9H_2Cl_6O_3$	239	0.86 mg/100 ml at 25 °C (estimated); readily soluble in acetone, benzene, and toluene; slightly soluble in water, *n*-hexane, and carbon tetrachloride
Tetrabromophthalic anhydride	632-79-1	463.71	$C_8Br_4O_3$	279.5–280.5	Insoluble in water and alcohol; slightly soluble in benzene and other organic solvents; soluble in nitrobenzene

CAS, Chemical Abstracts Service

[a] Physical and chemical properties of phthalic anhydride, trimellitic anhydride, maleic anhydride, hexahydrophthalic anhydride, methyl hexahydrophthalic anhydride, methyl tetrahydrophthalic anhydride, tetrahydrophthalic anhydride, and tetrachlorophthalic anhydride were derived from the source document. Properties for all other acid anhydrides were derived from the Hazardous Substances Data Bank (http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB).

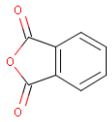
[b] 4-Methyl-delta 4-tetrahydrophthalic anhydride. Commercial products also contain the isomers 3-methyl-delta 4-tetrahydrophthalic anhydride ($MTHPA_{34}$) and 4-methyl-delta 3-tetrahydrophthalic anhydride ($MTHPA_{43}$) (Lindh & Jönsson, 1997).

3. ANALYTICAL METHODS

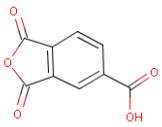
3.1 Sampling and analysis of workplace air

Solid sorbent tubes are used for the collection of samples of cyclic acid anhydride vapours (Tenax, XAD-2). A bubbler or impinger method is also possible. Both devices sample the anhydride as the corresponding acid. The impinger or bubbler method is also efficient for the sampling of particles, but not for small particles. Another possibility for sampling particles is the use of polyvinyl chloride (PVC) or Teflon filters in series with solid sorbent tubes. To recover both particles and vapours, sampling with both methods is recommended in studies where the state of exposure is unknown (Jönsson et al., 1996a,b).

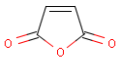
Gas chromatography (GC) with flame ionization detection (FID), electron capture detection (ECD), or mass spectrometric (MS) detection have been used for analysis of samples. Acetic anhydride may be added to the eluting solutions to increase the stability of the



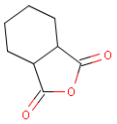
Phthalic anhydride



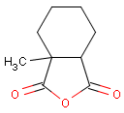
Trimellitic anhydride



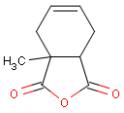
Maleic anhydride



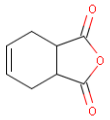
Hexahydrophthalic anhydride



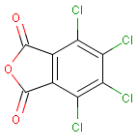
Methyl hexahydrophthalic anhydride



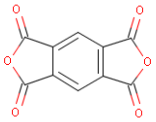
Methyl tetrahydrophthalic anhydride[44]



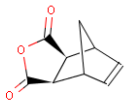
Tetrahydrophthalic anhydride



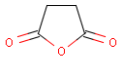
Tetrachlorophthalic anhydride



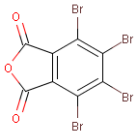
Pyromellitic dianhydride



Himic anhydride

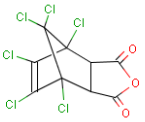


Succinic anhydride



Tetrabromophthalic anhydride

Dodecenylsuccinic anhydride



Chlorendic anhydride

Figure 1: Structures of selected acid anhydrides.

samples in the elution and analysis steps (Jönsson et al., 1996a,b).

Air samples of phthalic anhydride have been sampled with Tenax polymer tubes and analysed by GC using a ^{63}Ni-ECD. The limit of detection (LOD) was 0.4 µg/m^3 for a 12-litre sample (Pfäffli, 1986b, 1994). Phthalic anhydride can also be analysed as the corresponding phthalic acid by reversed-phase high-performance liquid chromatography (HPLC) (Nielsen et al., 1988).

The National Institute for Occupational Safety and Health (NIOSH) of the United States of America (USA) method for sampling and analysis of trimellitic anhydride utilizes a PVC copolymer membrane filter for sample collection. Following treatment of the filter with methanol and boron trifluoride, trimellitic anhydride is analysed as a trimethyl ester by GC-FID (NIOSH, 1994). Pfäffli (1994) modified the NIOSH method using a glass fibre filter in series with a Tenax tube. The analysis was conducted with GC-ECD. The detection limit was 0.6 µg/m^3 for 12 litres of air and a sampling rate of 0.2 l/min. Geyer et al. (1986) collected samples on glass fibre filters and converted the trimellitic anhydride to the acid with a 0.05 mol/l sodium hydroxide solution. Analysis was done by HPLC with an ultraviolet (UV) detector. The minimum quantifiable amount was 1 µg on a filter sample (sample size not given).

The NIOSH method of analysis for maleic anhydride draws a volume of air through a midget bubbler containing 15 ml of distilled water. The maleic acid is analysed by HPLC with a UV detector. The LOD is estimated to be 15 µg/m^3 per sample. The method does not distinguish between maleic anhydride and

maleic acid, and it has limited sample stability (NIOSH, 1994). Geyer & Saunders (1986) used a similar method with 0.1% phosphoric acid in distilled water as the absorbing solution. The minimum quantifiable concentration of maleic anhydride (measured as maleic acid) was 100 μg/m^3 for a 0.1 m^3 sample. The Occupational Safety and Health Administration (OSHA) of the USA describes a method in which sampling is performed on *p*-anisidine-treated XAD-2 and analysis is done using an ECD. The LOD is 0.1 μg/m^3 for a 12-litre sample.

Jönsson et al. (1991a, 1996a) reported a method using XAD-2 or a Tenax tube to sample hexahydrophthalic anhydride. Analysis was conducted with GC-FID. The LOD was 0.1 μg/ml of desorption solution. Glass fibre sampling gave results similar to those of the Tenax method (Jönsson et al., 1996b). Hexahydrophthalic anhydride has also been sampled with bubblers containing aqueous sodium hydroxide and analysed by GC-FID or electron ionization MS after conversion to dimethyl esters. The LOD using the electron ionization MS was 0.01 μg/sample with a 60-litre sample of air (Jönsson et al., 1991a, 1996a,b). A Fourier transform infrared spectrometer has been tested for the direct measurement of peak levels of hexahydrophthalic anhydride. The LOD was 120 μg/m^3 (Lindh et al., 1996).

Methyl hexahydrophthalic anhydride has been sampled with Tenax tubes and analysed with GC-ECD (Pfäffli et al., 1989). The LOD using XAD-2 tubes and GC-FID analysis was 0.1 μg/sample (sample volume not given). The LOD was the same for both the *cis* and *trans* isomers of methyl hexahydrophthalic anhydride (Jönsson et al., 1996b).

Methyl tetrahydrophthalic anhydride has been sampled using Amberlite XAD-2 solid sorbent tubes and analysed by GC-FID (Welinder & Gustavsson, 1992). The LOD for air samples was 10 μg/m^3 for a 20-litre sampling volume. The sensitivity was the same for the isomers in the technical grade (Lindh & Jönsson, 1994). Johyama et al. (1999) used silica gel tubes for the sampling and GC-ECD for the analysis of methyl tetrahydrophthalic anhydride. Concentrations above 1.0 μg/m^3 were quantified after 20 min of sampling with a sampling rate of 1 l/min.

Tetrahydrophthalic anhydride has been sampled with XAD-2 tubes and analysed with GC-FID. The detection limit was 0.1 μg/sample; the sample volume was not given (Jönsson et al., 1996b).

3.2 Analysis of urine and plasma samples

Pfäffli et al. (1989) reported a method for determining the dicarboxylic acids of phthalic anhydride, hexahydrophthalic anhydride, methyl hexahydrophthalic anhydride, and tetrahydrophthalic anhydride in urine. The acids were esterified with 2,2,2-trichoroethanol and analysed by GC-MS. The detection limits were 2–4 ng/ml urine for aliphatic and alicyclic acids and 15 ng/ml for phthalic acid.

Pfäffli (1986a) collected urine samples from phthalic anhydride–exposed workers pre-shift, post-shift, in the evening, and on the following morning. The samples were esterified with boron trifluoride and methanol and analysed with GC-ECD. The LOD was 0.05 μmol/l (10-ml urine samples). A significant correlation was found between the phthalic acid concentration in the urine samples and the atmospheric phthalic acid concentrations. When the exposure level was about 1800 μg/m^3, the body burden was not eliminated overnight.

For hexahydrophthalic anhydride–exposed workers, a correlation was found between time-weighted levels of hexahydrophthalic anhydride in the air and concentrations of hexahydrophthalic acid in post-shift urine (r_s = 0.93, $P < 0.023$). The LOD in urine was 20 ng/ml. The method used esterification with methanol and boron trifluoride and GC-MS. The authors estimated that with this method it is possible to monitor hexahydrophthalic anhydride concentrations in air of approximately 1–2 μg/m^3 (Jönsson & Skarping, 1991; Jönsson et al., 1991b).

Lindh & Jönsson (1994) further developed this method for the analysis of methyl tetrahydrophthalic acid in urine. The overall LOD for three isomers of commercial-grade methyl tetrahydrophthalic anhydride was <6 ng/ml.

Jönsson & Lindh (1996) developed the method to be less labour intensive and capable of LODs in urine for hexahydrophthalic acid and methyl hexahydrophthalic acid of 11 ng/ml and 17 ng/ml, respectively.

Lindh & Jönsson (1997) developed a method to measure hexahydrophthalic acid and methyl hexahydrophthalic acid simultaneously in plasma. The LODs were 0.4 ng/ml and 0.3 ng/ml for hexahydrophthalic acid and methyl hexahydrophthalic acid, respectively.

4. SOURCES OF HUMAN EXPOSURE

Organic acid anhydrides are human-made chemicals commercially available at high purity as liquids or crystals, depending on the type of anhydride. They are not found in nature, but may be found as environmental contaminants (Venables, 1989).

The annual world production of phthalic anhydride has been about 2 200 000 tonnes during the past decade, of which European production was about 820 000 tonnes. Phthalic anhydride production in 1996 was about 830 000 tonnes in Asia, about 420 000 tonnes in North America, and about 150 000 tonnes in South America. Belgium, the USA, and Italy are the primary countries producing maleic anhydride. In 1997, they produced 58 000, 44 000, and 25 000 tonnes, respectively (United Nations Economic Commission for Europe, 1998).

The cyclic acid anhydrides are used mainly in the manufacture of polyester and alkyd resins and plasticizers and as epoxy resin hardeners. Workers are exposed to acid anhydrides in powder form during various manufacturing processes, such as during synthesis or when the acid anhydrides are used as starting agents for thermosetting products. Workers are also exposed to anhydride fumes in hot processes, such as when epoxy resins are hardened, polyester paints are cured, alkyd or polyester painted metal surfaces are welded, or the paints are burned from surfaces.

5. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

There are no data available on the transport, distribution, or transformation of cyclic acid anhydrides in the environment in the source document. The following information for phthalic anhydride was obtained from the United States Environmental Protection Agency's (USEPA) Office of Pollution Prevention and Toxics (USEPA, 1994).

No information is available on the atmospheric transport of phthalic anhydride. The water solubility of phthalic anhydride suggests that wet deposition may occur before it is converted to the less soluble phthalic acid.

No information is available on the aquatic transport of phthalic anhydride. Because phthalic anhydride undergoes rapid hydrolysis to phthalic acid in aqueous media, there would be no significant transport of the parent compound. The low vapour pressure (0.069 Pa) and Henry's Law constant (1.6×10^{-3} Pa·m^3/mol) indicate slow volatilization from water. Its high solubility (6200 mg/l at 25 °C) and low sorption coefficient (K_{oc}, estimated to be 36) indicate low potential for sedimentation and adsorption to particles, respectively.

No information is available on the transport of phthalic anhydride in soil. In moist soil conditions, phthalic anhydride will hydrolyse to phthalic acid. Significant leaching is unlikely to occur, except in the case of a large spill. Volatilization from soil is unlikely, based on the low vapour pressure.

Phthalic anhydride will react with hydroxyl radicals in the atmosphere, and the rate constant is estimated to be 5.0×10^{-13} cm^3/molecule per second. Assuming that the atmospheric concentration of hydroxyl radicals is 10^6 molecules/cm^3, the estimated half-life for this reaction is 21 days.

Phthalic anhydride is expected to biodegrade in soil. In aerobic soil conditions, phthalic anhydride has an estimated half-life of >14 days.

Phthalic anhydride may significantly degrade in water by hydrolysis and biodegradation. The hydrolytic half-life is ~1.5 min. Biodegradation values estimated by the USEPA for various wastewater treatment conditions are as follows: 1) 44–78% mineralization in 5 days based on theoretical biological oxygen demand; 2) ~21% degradation in 5 days using standard wastewater treatment dilution methods; 3) ~18% degradation using the seawater dilution method; 4) 33% degradation in 24 h using chemical oxygen demand removal; and 5) >30% degradation in 2 weeks using the Japanese Ministry of International Trade and Industry (MITI) test. In the river die-away test using Mississippi River (USA) water, phthalic acid was 50% degraded in 1.5 weeks.

6. HUMAN EXPOSURE

6.1 Occupational exposure

Exposure data for the workplace are limited, and measurements have been prompted by work-related health problems. When filters are not used in the sampling, exposure in particulate form may be missed. The highest exposure levels have been found in flaking, sacking, loading of reactors, and charging with anhydrides in solid form, especially with phthalic anhydride, tetrachlorophthalic anhydride, and trimellitic anhydride. The exposure levels from the last decade have generally been lower than earlier exposure levels, pointing to the awareness of the harmful effects and to improved occupational hygiene. Anhydride vapours and sublimates are found in the work atmosphere when products containing anhydrides are heated. Often several anhydrides as well as other sensitizing or irritating agents are included in the processes, making the exposure more difficult to assess.

Early measurements of phthalic anhydride taken during production found very high exposure levels (320–17 400 µg/m^3), especially when "process difficulties"

and the loading of reactors occurred (Pfäffli, 1986b; Nielsen et al., 1988). In a more recent study, in which both particles and vapours were sampled, the full-shift personal samples taken during the production of alkyd resins contained 10- to 100-fold lower concentrations, although peak phthalic anhydride concentrations were up to 1860 μg/m^3 (Van Tongeren et al., 1995).

Exposure measurements of trimellitic anhydride carried out during the manufacture of cushioned flooring found that the highest exposure levels occurred when both particles and vapours were sampled (150–20 433 μg/m^3). Otherwise, only a few values were above the occupational exposure limit of 40 μg/m^3. The results were based on only 1–4 samples per task, however (Van Tongeren et al., 1995).

The exposure levels of maleic anhydride have been low, even in charging in the production of alkyd resins (Van Tongeren et al., 1995).

In two plants that performed epoxy resin isolation, methyl hexahydrophthalic anhydride concentrations of 130–500 μg/m^3 were found. In one of the plants, exposure levels up to 403 μg methyl hexahydrophthalic anhydride/m^3 were found in casting. In casting, solid or semisolid anhydride curing agents (methyl tetrahydrophthalic anhydride, hexahydrophthalic anhydride, and methyl hexahydrophthalic anhydride) are heated, and the compounds are vaporized. The major exposure in these industries may derive from leakages from ovens during the subsequent curing step (Welinder et al., 1994).

When epoxy resin was handled in the wet part of the process in the manufacture of barrels, methyl tetrahydrophthalic anhydride concentrations of 380 μg/m^3 were measured, but exposure levels up to 3000 μg methyl tetrahydrophthalic anhydride/m^3 were found close to the heated, wet material before curing (Welinder et al., 1990).

Concentrations of methyl tetrahydrophthalic anhydride during the processes of assembling and hardening in condenser manufacture were found to be between 36.5 and 695 μg/m^3 (geometric mean) (Johyama et al., 1999).

Exposure concentrations of 140–590 μg tetrachlorophthalic anhydride/m^3 were measured in a workplace where solenoid coils were being manufactured. The compound had been used to cure epoxy resin. After improvements in work hygiene, the concentrations decreased to <10–110 μg/m^3 (Liss et al., 1993).

When products containing rest monomers (i.e. unreacted starting material) or esters of cyclic *ortho*-dicarboxylic acids are heated, anhydrides tend to be released and sublimate into the ambient air. This problem occurs in several work processes, such as in the curing of polyester powder paints containing unsaturated polyesters at elevated temperatures. Phthalic anhydride has been detected when diethylhexyl phthalate, an ester plasticizer, is heated (Pfäffli, 1986b). Cyclic anhydrides have also been detected in welding fumes from painted steel (Henriks-Eckerman et al., 1990; Keskinen et al., 2000).

6.2 Consumer exposure

Moffitt & Sansom (2002) reported a case of a 33-year-old woman who presented with allergic contact dermatitis. Patch tests revealed a positive reaction to phthalic anhydride/trimellitic anhydride/glycols copolymer (1%) ingredient present in nail varnish. This is the only report of consumer exposure to cyclic acid anhydrides.

7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

7.1 Absorption

Five healthy human volunteers were exposed to hexahydrophthalic anhydride at 80 μg/m^3 for 8 h (Jönsson & Skerfving, 1993). During exposure, 1–4% was found in exhaled air. Jönsson & Skarping (1991) collected and analysed urine for 24 h from a worker exposed to an 8-h time-weighted average concentration of 30 μg/m^3. Greater than 85% of the inhaled dose was excreted in urine as hexahydrophthalic acid.

Jönsson et al. (1993) evaluated the percutaneous absorption of hexahydrophthalic anhydride applied to the back skin of three human volunteers for 48 h. The test chemical was administered in petrolatum. Urine was collected from the volunteers for 72 h. The excreted amounts of hexahydrophthalic acid were between 1.4% and 4.5%, 0.2% and 1.3%, and 0% and 0.4% of the total applied dose for the three subjects, respectively, indicating minimal absorption of the anhydride. The subject with the highest excretion of hexahydrophthalic acid (1.4–4.5%) exhibited pale erythema after removal of the test chemical, suggesting that inflamed skin may permit higher absorption.

No human data are available on the oral or gastrointestinal absorption of cyclic acid anhydrides.

7.2 Distribution

Lindh et al. (1999) evaluated the distribution of hexahydrophthalic anhydride in guinea-pigs and rats

exposed via inhalation to ($^3H_2$)-hexahydrophthalic anhydride for 3–8 h (concentration not provided). Autoradiography was used to localize the radioactivity levels in tissues. Lung tissue contained negligible levels of radioactivity, whereas the mucosa of the nasal region and trachea contained medium to high levels. The gastrointestinal tract and conjunctiva possessed tissue-bound radioactivity, although the amount was not described. Low levels of tissue-bound radioactivity were found in the kidney cortex of rats, but not guinea-pigs. Radioactivity persisted for at least 7 days after the end of exposure. Tissue-bound radioactivity could be only partially extracted by organic solvents and water, suggesting that radioactive chemical was covalently bound to tissue macromolecules. Radioactivity in dialysed plasma was primarily found in the same fraction as albumin.

7.3 Metabolism and excretion

The anhydride moiety of acid anhydrides readily reacts with amino acids and conjugates with proteins, as has been demonstrated with human serum albumin (Zeiss et al., 1977; Taylor et al., 1987). In an in vitro experiment at 37 °C, trimellitic anhydride rapidly conjugated with human serum albumin in 1 min (Zeiss et al., 1977).

Sera from hexahydrophthalic anhydride– and methyl hexahydrophthalic anhydride–exposed workers have measurable plasma protein and albumin adduct levels that correlated with exposure (Rosqvist et al., 2000). The half-time for these adducts in vivo was about 20 days.

In vitro and in vivo exposure tests on guinea-pig lung found that methyl tetrahydrophthalic anhydride was conjugated primarily to lysine in the collagen (Jönsson et al., 1995). Experiments using human erythrocytes exposed to hexahydrophthalic anhydride or methyl hexahydrophthalic anhydride demonstrated conjugation with haemoglobin. The major amino acid bound to hexahydrophthalic anhydride was lysine (Lindh & Jönsson, 1998).

Acid anhydrides are excreted in urine as the corresponding dicarboxylic acids.

Blood samples from workers exposed to methyl hexahydrophthalic anhydride concentrations of 140–310 μg/m^3 had end of work shift levels of 3.4–10.7 nmol/l (Pfäffli & Savolainen, 1991). The same *cis* form of methyl hexahydrophthalic anhydride in the exposure was found in the blood samples; no free acids were detected.

Pfäffli (1986a) monitored the excretion of phthalic acid in workers exposed to phthalic anhydride by sampling pre-shift, on-shift, post-shift, evening, and following-morning urine. Low atmospheric exposure to phthalic anhydride (150 μg/m^3; range 30–330 μg/m^3) resulted in pre-shift urine concentrations of phthalic acid at the same level as for occupationally unexposed workers (0.34 μmol/mmol creatinine; range 0.02–0.89 μmol/mmol creatinine). Workers exposed to higher concentrations of phthalic anhydride (1630 ± 130 μg/m^3) demonstrated an accumulation of urinary phthalic acid. Pre-shift urinary phthalic acid in these workers was 1.02 ± 0.25 μmol/mmol creatinine. At exposure concentrations of 10 500 μg/m^3, pre-shift urinary phthalic acid levels were 4.8 μmol/mmol creatinine, which is approximately 14-fold greater than that observed in workers with low exposure. No glucuronide conjugates of phthalic acid were observed.

Jönsson & Skarping (1991) reported that the urinalysis of one worker exposed to 30 μg hexahydrophthalic anhydride/m^3 (time-weighted average) demonstrated that >85% of the inhaled amount was excreted as hexahydrophthalic acid.

The half-time of phthalic acid in urine of phthalic anhydride–exposed workers was approximately 14 h (Pfäffli, 1986a). The half-times of corresponding dicarboxylic acids were assumed to be 7 h for workers exposed to low levels of methyl hexahydrophthalic anhydride and 14 h for workers exposed to hexahydrophthalic anhydride and tetrahydrophthalic anhydride (Pfäffli et al., 1989). Pfäffli et al. (1989) also reported that an input–output equilibrium between methyl hexahydrophthalic anhydride and its urinary acid was reached after 4 h of exposure to a concentration of 116 μg/m^3. Jönsson & Skarping (1991) reported a half-time of 2–3 h for hexahydrophthalic acid in urine in hexahydrophthalic anhydride–exposed workers. Jönsson & Skerfving (1993) reported half-times of 1.7–1.8 h for hexahydrophthalic acid in plasma of two male volunteers exposed to hexahydrophthalic anhydride at a concentration of 80 μg/m^3 for 8 h. Lindh & Jönsson (1994) performed urinalysis of a worker exposed to commercial methyl tetrahydrophthalic anhydride and reported half-times of 3, 3, and 6 h for the three isomers, 3-methyl-delta 4-tetrahydrophthalic anhydride, 4-methyl-delta 4-tetrahydrophthalic anhydride, and 4-methyl-delta 3-tetrahydrophthalic anhydride, respectively.

The studies summarized in this section demonstrate that cyclic acid anhydrides bind to plasma proteins and haemoglobin and that the primary binding amino acid appears to be lysine. The half-time of methyl hexahydrophthalic anhydride adducts was 20 days. Cyclic acid anhydrides are hydrolysed to corresponding dicarboxylic acids and effectively excreted in urine. The urinary half-time for the dicarboxylic acid of phthalic anhydride was 14 h, whereas half-times for the dicarboxylic acids of

Table 2: Mean lethal doses (LD_{50} values) and concentrations (LC_{50} values) for cyclic acid anhydrides.

Acid anhydride	Species	Route of administration	LD_{50} (mg/kg bw) or LC_{50} (mg/m^3)	Reference
Phthalic anhydride	Cat	Oral	800	NIOSH (2001)
	Rat	Oral	1530	NIOSH (2001)
	Mouse	Oral	1500	NIOSH (2001)
	Mouse	Intraperitoneal	75.5	Fabro et al. (1982)
Trimellitic anhydride	Mouse	Oral	1900	Batyrova & Uzhdavini (1970)
	Rat	Oral	2730	OECD (2002)
	Rabbit	Oral	5600	NIOSH (2001)
	Rat	Inhalation	2330	OECD (2002)
	Rabbit	Dermal	>2000	OECD (2002)
	Rat	Dermal	5600	OECD (2002)
Maleic anhydride	Rat	Oral	400	NIOSH (2001)
	Guinea-pig	Oral	390	NIOSH (2001)
	Mouse	Oral	465	NIOSH (2001)
	Rabbit	Oral	875	NIOSH (2001)
	Rabbit	Dermal	2620	Vernot et al. (1977)
	Rat	Intraperitoneal	97	NIOSH (2001)
Methyl tetrahydrophthalic anhydride	Rat	Oral	2140	Smyth et al. (1969)
Tetrahydrophthalic anhydride	Rat	Oral	5410	Sax & Lewis (1987)
Tetrachlorophthalic anhydride	Rat	Oral	>15 800	Sax & Lewis (1987)
	Rabbit	Dermal	<5000	Sax & Lewis (1987)

hexahydrophthalic anhydride, methyl hexahydrophthalic anhydride, and methyl tetrahydrophthalic anhydride were generally shorter (between 2 and 7 h).

8. EFFECTS ON LABORATORY MAMMALS AND IN VITRO TEST SYSTEMS

8.1 Single exposure

Acute lethality data for cyclic acid anhydrides are presented in Table 2. Phthalic anhydride and maleic anhydride have the lowest median lethal doses (LD_{50} values). In rats, the oral LD_{50} values were 1530 mg/kg body weight (bw) for phthalic anhydride and 400 mg/kg bw for maleic anhydride. Tetrachlorophthalic anhydride is the least acutely toxic anhydride, with an LD_{50} of >15 800 mg/kg bw in rats by oral administration.

8.2 Short-term exposure

Only one short-term exposure study was reported. This study demonstrated that oral tetrachlorophthalic anhydride at doses of 25 000, 100 000, 250 000, or 500 000 µg/kg bw in corn oil for 7 days is a weak but wide-spectrum inducer of microsomal enzymes in rats (Ridley et al., 1988). This effect was not observed in mice.

8.3 Medium-term exposure

In a 6-month study of maleic anhydride vapour inhalation by rats (15 per sex per group), hamsters (15 per sex per group), and monkeys (3 per sex per group) at a concentration range of 1100–9800 µg/m^3, no exposure-related effects were observed in histopathological evaluations of lungs, liver, spleen, bone marrow, and kidneys (Short et al., 1988). Histopathological evaluation of nasal tissue from rats and hamsters revealed irritation in the form of hyperplasia and metaplasia. Metaplastic effects consisted of the cuboidal to low columnar epithelium becoming hyperplastic and pseudostratified. In addition, transformation to non-keratinizing squamous-type epithelium was observed. Metaplastic effects were observed at all dose levels with a non-linear increase in incidence. All three species displayed inflammatory changes in nasal tissue. However, these effects were determined to be reversible. There was no evidence of systemic toxicity attributable to maleic anhydride.

Rats exposed to hexahydrophthalic anhydride vapours at 34 300, 68 600, or 137 300 µg/m^3 for 6 h/day, 5 days/week, for 2–11 weeks exhibited significantly decreased cerebral and cerebellar acetylcholinesterase activity at the 137 300 µg/m^3 exposure after 2 weeks, compared with controls (Savolainen & Pfäffli, 1986). After 11 weeks, these activities had normalized to control levels. Creatine kinase activity was increased in cerebellar tissue after 11 weeks of exposure.

Rats exposed to 1000–10 000 mg trimellitic anhydride/kg in the diet (50–500 mg/kg bw per day) for 90 days did not exhibit any adverse effects (Hill Top Research, 1969a; IBT, 1970; OECD, 2002). Leukocyte counts demonstrated a dose-dependent increase (no-observed-effect level [NOEL] = 50 mg/kg bw per day) in rats from one study (Hill Top Research, 1969a), but not in the second study (IBT, 1970). However, the elevated leukocyte counts may have been due to the increased incidence of bronchitis, peribronchitis, and/or focal pneumonia reported in both treatment and control groups (OECD, 2002). A 13-week study in dogs (Hill Top Research, 1969b) exposed to 1000–20 000 mg/kg in the diet (25–500 mg/kg bw per day) demonstrated a slight increase in adrenal weight. This study was insufficient to assess the significance of this end-point, as only two dogs per dose were used (OECD, 2002).

8.4 Long-term exposure and carcinogenicity

Information on the carcinogenicity of cyclic acid anhydrides is scarce. Long-term feeding studies of phthalic anhydride in rodents provided no evidence of carcinogenicity (Kluwe et al., 1982; Shelby & Stasiewicz, 1984; Kluwe, 1986; Haseman et al., 1987). No other end-points were reported in these studies.

In a limited study of six rats, subcutaneous injection of 2000 µg succinic anhydride in 0.5 ml arachis oil, twice per week for 65 weeks, resulted in subcutaneous sarcomas at the injection site in the three rats that survived 93–106 weeks (IARC, 1977). No tumours were observed in the 24 control rats that survived 45–106 weeks and were injected with only arachis oil. No other end-points were reported in these studies.

8.5 Genotoxicity and related end-points

No mutagenicity in the Ames test using *Salmonella typhimurium* was observed for phthalic anhydride, tetrachlorophthalic anhydride, tetrabromophthalic anhydride, or trimellitic anhydride (Macgregor & Friedman, 1977; Zeiger et al., 1985; OECD, 2002). Phthalic anhydride and tetrachlorophthalic anhydride were negative for chromosomal aberrations in in vitro assays using Chinese hamster ovary cells or rat liver cells (Phillips et al., 1986; Galloway et al., 1987). Chinese hamster ovary cells were also tested for sister chromatid exchanges using phthalic anhydride and tetrachlorophthalic anhydride and were negative (Galloway et al., 1987). In a later chromosomal aberration test using a higher and cytotoxic concentration of phthalic anhydride (10 mmol/l), there was an 18.5% increase in aberrations compared with 3% in controls (Hilliard et al., 1998). Trimellitic anhydride was negative for mutagenicity in *S. typhimurium* (TA98, TA100, TA1535, and TA1537) in the presence and absence of a metabolic activation system (rat liver S9) (San & Wagner, 1991). Trimellitic anhydride was also negative for *HGPRT* mutations and chromosomal aberrations in Chinese hamster ovary cells both with and without metabolic activation (Bigger & Sigler, 1991; Putnam & Morris, 1991). No additional genotoxicity or mutagenicity data were reported.

8.6 Reproductive and developmental toxicity

CD-1 mice orally administered trimellitic anhydride (550 000 µg/kg) during gestation days (GD) 7–14 did not exhibit any effects (Hazelden, 1983). Guinea-pigs exposed by inhalation to trimellitic anhydride at 0.5 mg/m^3 during GD 6–15 did not exhibit any signs of fetotoxicity or teratogenicity (Ryan, 1988; OECD, 2002). This study also found that similarly treated pregnant rats exhibited increased antibody levels. Neonatal rats exhibited increased antibody levels but no fetotoxicity or teratogenicity. A challenge exposure resulted in lung foci only in offspring whose mothers had not recovered from the trimellitic anhydride exposure. Lung foci were not observed in adult offspring.

Phthalic anhydride and succinic anhydride were evaluated for teratogenicity in mice by daily intraperitoneal injections of 0.2–0.6 mmol/kg bw per day on GD 8–10 (Fabro et al., 1982). Malformations were observed only at exposure levels producing maternal toxicity.

Rats treated orally with maleic anhydride at a dose of 140 000 µg/kg bw per day during GD 6–15 did not exhibit any treatment-related effects on fetal development (Short et al., 1986). In a two-generation study, no treatment-related effects on reproduction were observed for maleic anhydride at doses up to 55 000 µg/kg bw per day (Short et al., 1986).

8.7 Other toxicity

The irritation and sensitization effects of cyclic acid anhydrides are the major occupational concern in humans. Studies in this section discuss the animal studies that have evaluated these end-points.

8.7.1 Irritation

Animal studies have demonstrated that maleic anhydride and trimellitic anhydride exhibit greater irritation effects than does phthalic anhydride (Table 3). A 50% solution of phthalic anhydride in oil did not irritate rabbit ears after 20 h of exposure (DFG, 1986/1987). Potokar et al. (1985) reported that a dermal patch application of 500 mg of phthalic anhydride for 1 or 4 h did not cause irritation on rabbit skin assessed 1, 24, 48, and 72 h or 7 days later. On rabbit eyes, one drop of phthalic anhydride (5%) in polyethylene glycol 400 was slightly irritating, whereas a 0.5% solution was not (DFG, 1986/1987). Gad et al. (1986) reported that phthalic anhydride was a mild skin irritant and a moderate eye irritant. Batyrova & Uzhdavini (1970) reported that trimellitic anhydride (50%) caused slight and reversible dermatitis in mice and rats after either a single or repeated dermal exposure for 2 h.

Animal experiments have demonstrated that maleic anhydride and trimellitic anhydride are extremely strong eye irritants. Application of 1% maleic anhydride to the eyes of rabbits resulted in cloudiness of the cornea and hyperaemia of the conjunctiva within a few minutes (Winter & Tullius, 1950). Eyes were normal by the following morning. A 5% solution of maleic anhydride produced more intense irritation that lasted 1 week. Application of maleic anhydride powder in minute amounts caused long-lasting damage and corneal vascularization in rabbit eyes. Application of 50 mg of trimellitic anhydride powder to rabbit eyes caused reversible hyperaemia of the conjunctiva, lacrimation, and blepharospasms (Batyrova & Uzhdavini, 1970).

Arts et al. (2001) evaluated trimellitic anhydride–induced respiratory irritation in Brown Norway and Wistar rats. The rats were exposed for 30 min to concentrations ranging from 10 to 300 mg/m^3. The Brown Norway rats exhibited breathing pattern changes at concentrations of ≥29 mg/m^3 and decreases in breathing frequency at ≥60 mg/m^3. Wistar rats exhibited these breathing pattern and frequency effects at ≥34 mg/m^3. These changes were reversible and considered to be suggestive of lower airway irritation rather than upper airway irritation. The highest concentration at which no airway irritation was observed in both rat strains was 14 mg/m^3.

Short et al. (1988) conducted a 6-month inhalation study of maleic anhydride in rats, hamsters, and monkeys. Exposures were 0, 1100, 3300, or 9800 µg/m^3 for 6 h/day, 5 days/week. Ocular irritation and nasal irritation were observed at all dose levels in a concentration-dependent manner. Histopathological evaluation of nasal tissue revealed irritation such as hyperplasia and metaplasia in rodents and inflammatory changes in all three species. However, all effects were determined to be reversible.

8.7.2 Allergic contact dermatitis

A closed patch test in guinea-pigs (Buehler test) and the mouse ear swelling test demonstrated that phthalic anhydride was a moderate sensitizer (Gad, 1988). Several studies have been conducted to evaluate cytokine production patterns following topical sensitization (Dearman & Kimber, 1991, 1992; Dearman et al., 2000). These studies found that phthalic anhydride, trimellitic anhydride, maleic anhydride, hexahydrophthalic anhydride, and methyl tetrahydrophthalic anhydride were negative in inducing type IV contact allergy.

8.7.3 Antibody-mediated sensitization

Antibody-mediated sensitization studies are summarized in Table 4. The studies described in this section demonstrate that antibody responses have been induced by cyclic acid anhydrides via bronchial, subcutaneous, intradermal, and parenteral routes of exposure. Development of an allergic respiratory disease is dependent on the production of specific antibodies. Some of the studies described in this section demonstrate the development of allergic respiratory responses following sensitization with cyclic anhydrides.

Sarlo et al. (1994) sensitized guinea-pigs to phthalic anhydride dust by inhalation exposure to 500, 1000, or 5000 µg/m^3 for 3 h/day for 5 consecutive days. The guinea-pigs were challenged after 2 weeks with phthalic anhydride–guinea-pig serum albumin (2000 µg/m^3) and displayed immediate respiratory reactions, as determined by plethysmography. Inhalation challenge with phthalic anhydride dust (5000 µg/m^3) did not cause an immediate reaction, although the guinea-pigs had a significant number of haemorrhagic lung foci. These lung foci were not observed in the animals challenged with phthalic anhydride–guinea-pig serum albumin. Anti-phthalic anhydride–guinea-pig serum albumin immunoglobulin G (IgG) was detected in sera of all exposed animals, with a significant dose–response relationship.

Zeiss et al. (1987) conducted an inhalation experiment by exposing rats to trimellitic anhydride dust at concentrations of 0, 10, 30, 100, or 300 µg/m^3 for 6 h/day for 5 or 10 days. Exposure levels of 30–300 µg/m^3 for 10 days caused haemorrhagic lung foci. Anti-trimellitic anhydride–rat serum albumin antibody binding was correlated with exposure concentration, the presence of haemorrhagic lung foci, and lung weight. By 12 days post-exposure, the lung lesions healed, although a repeated exposure caused a return of lesions (Zeiss et al., 1987). Histological evaluation of the lung lesions indicated extensive cellular infiltration of primarily macrophages, alveolar haemorrhage, and pneumonitis.

Table 3: Irritation effects of phthalic anhydride, trimellitic anhydride, and maleic anhydride.

Acid anhydride	Species	Route of administration	Exposure data	Effect	Reference
Phthalic anhydride	Rabbit	Eye application	50 mg	Moderate irritation	NIOSH (2001)
	Rabbit	Eye application	0.5% or 5%	Slight irritation at 5%	DFG (1986/1987)
	Rabbit	Dermal patch	500 mg (1 or 4 h)	No skin irritation	Potokar et al. (1985)
	Rabbit	Dermal, ears	50% (20 h)	No irritation	DFG (1986/1987)
Trimellitic anhydride	Rabbit	Eye application	50 mg	Conjunctival hyperaemia, lacrimation	Batyrova & Uzhdavini (1970)
Maleic anhydride	Rabbit	Eye application	1% and 5%	Cloudiness of cornea and conjunctival hyperaemia	Winter & Tullius (1950)

Table 4: Summary of antibody-mediated sensitization studies in animals exposed to cyclic acid anhydrides.

Acid anhydride/ species	Route of administration	Exposure	Effect	Reference
Phthalic anhydride				
Guinea-pig	Inhalation	500, 1000, or 5000 µg phthalic anhydride dust/m^3, 3 h/day for 5 days; challenged with phthalic anhydride (5000 µg/m^3) or phthalic anhydride–guinea-pig serum albumin (2000 µg/m^3)	IgG antibodies in lowest exposure > air exposure control; dose–response of IgG antibodies; haemorrhagic lung foci in highest exposure and phthalic anhydride challenge	Sarlo et al. (1994)
Rabbit	Subcutaneous	0.25 ml phthalic anhydride–rat serum albumin/week for 12 weeks	High IgG titre to phthalic anhydride–rat serum albumin and phthalic anhydride–human serum albumin	Hatanaka et al. (1997)
Mouse	Cutaneous	Phthalic anhydride 4:1 in acetone:olive oil, 50 µl on both flanks; after 7 days, 1:1 dilution of 25 µl × 2 on both ears	IgE elevated after 14 days; IgE antihapten antibodies; IgG_{2b} antihapten antibodies	Dearman & Kimber (1992)
Rat	Intradermal	0.1 ml of 0.2 mol phthalic anhydride/l	Specific IgE and IgG antibodies	Zhang et al. (1998b)
Trimellitic anhydride				
Guinea-pig	Intravenous immunization; inhalation challenge	21–28 days after immunization challenge with 50 µl 1% trimellitic anhydride–guinea-pig serum albumin	Specific IgG_1 and IgE antibodies; increased lung resistance and airway microvascular leakage	Hayes et al. (1992a)
Guinea-pig	Intradermal	0.1 ml of 30% trimellitic anhydride	Specific IgE and IgG antibodies	Botham et al. (1989)
Guinea-pig	Intradermal immunization; intratracheal challenge	Immunization with 0.1 ml of 0.3% trimellitic anhydride; challenge with 50 µl 0.5% trimellitic anhydride–guinea pig serum albumin at 1, 2, 3, 5, or 8 weeks after immunization	Increased lung resistance, extravasation, and specific IgG_1 antibodies, which correlated with extravasation	Arakawa et al. (1993b)

Table 4 (continued)

Acid anhydride/ species	Route of administration	Exposure	Effect	Reference
Rat	Inhalation	10–300 µg dust/m^3, 6 h/day for 5 or 10 days	At ≥30 µg/m^3, haemorrhagic lung foci and trimellitic anhydride–rat serum albumin antibodies after 10 days	Zeiss et al. (1987)
Rat	Inhalation	100 µg powder/m^3, 6 h/day, 5 days/week for 2 weeks	Haemorrhagic foci, antibodies in bronchoalveolar lavage fluid, and detection of anti-trimellitic anhydride–rat serum albumin IgG, IgA, and IgM	Chandler et al. (1987)
Rat	Inhalation	330 µg powder/m^3, 6 h/day on days 1, 5, and 10; challenge on day 22 for 6 h with 330 µg powder/m^3	Fewer haemorrhagic lung foci in unchallenged compared with challenged animals; lung injury correlated with antibodies in challenged animals	Zeiss et al. (1989)
Rat	Inhalation	500 µg powder/m^3, 6 h/day on days 1, 5, and 10; challenge on day 29, 6 h to 540 µg/m^3	IgG–, IgM–, and IgA–trimellitic anhydride–rat serum albumin antibodies; haemorrhagic foci, mean 216 per lung	Zeiss et al. (1989)
Rat	Inhalation	500 µg powder/m^3, 6 h/day on days 1 and 5; challenge on day 29, 6 h to 500 µg/m^3	Haemorrhagic foci, mean 112 per lung, good correlation with antibody activity (P = 0.027)	Zeiss et al. (1989)
Rat	Intradermal immunization; inhalation challenge	After 3 weeks' challenge with 0.003% or 0.03% trimellitic anhydride–rat serum albumin (15 min) in 1 or 7 days	High levels of specific IgE and IgG; significant rise in bronchial hyperreactivity after repeated challenges; slight damage to airway epithelium in repeat-challenged groups	Cui et al. (1997)
Rat	Inhalation	0.04, 0.4, 4, or 40 mg aerosol/m^3, 10 min, once per week for 10 weeks; challenged with 40 mg/m^3	Specific IgE response, early- and late-phase airway responses, and histopathological changes	Zhang et al. (2006)
Rat	Dermal sensitization; inhalation challenge	Sensitization with 50% w/v and then 25% w/v trimellitic anhydride; inhalation challenge 0.2–250 mg/m^3	Elevated total IgE, laryngeal inflammation, squamous epithelial metaplasia, pulmonary haemorrhages, increase in nonspecific airway responsiveness, decrease in breathing frequency	Arts et al. (2004)
Rat	Intradermal sensitization; inhalation challenge	Sensitization with 1, 5, or 25% trimellitic anhydride applied 2 times at weekly intervals, challenge with 25–30 mg trimellitic anhydride at 17, 24, 41, 47, 55, and 56 days after sensitization	In groups sensitized with ≥5%, altered breathing patterns and increased airway responsiveness	Pauluhn (2003)
Mouse	Inhalation	5000 µg dust/m^3, 1 h/day for 3 days	IgG–trimellitic anhydride–mouse serum albumin antibodies after 1 week, IgE–trimellitic anhydride–mouse serum albumin antibodies after 2 weeks	Dearman et al. (1991)
Hexahydrophthalic anhydride or methyl tetrahydrophthalic anhydride				
Guinea-pig	Intradermal immunization; inhalation challenge	Four weeks after immunization, challenged with hexahydrophthalic anhydride– or methyl tetrahydrophthalic anhydride–guinea-pig serum albumin, 3 ml (nebulizer) or 0.01–1000 µg/kg bw (intravenous)	Decrease in static compliance and arterial oxygen level, increase in inspiratory resistance after 10 min; critical dose 40 µg/kg bw	Zhao et al. (1997)

w/v, weight by volume

These effects presented in a dose-dependent manner. The lungs were the only affected organs (Leach et al., 1987).

Chandler et al. (1987) exposed rats by inhalation to trimellitic anhydride powder at a concentration of 100 μg/m^3 for 6 h/day, 5 days/week, for 2 weeks. At autopsy, the surface of the lungs had haemorrhagic foci. Higher total antibody concentrations were observed in the bronchoalveolar lavage fluid than in serum. Anti-trimellitic anhydride–rat serum albumin IgG, IgA, and IgM were detected (Chandler et al., 1987). Antibody levels in bronchoalveolar lavage and serum were highly correlated with lung injury (Zeiss et al., 1988).

In two separate studies, Zeiss et al. (1989) exposed rats by inhalation to trimellitic anhydride powder at concentrations of 330 or 500 μg/m^3 on days 1, 5, and 10 for 6 h/day and challenged the rats with trimellitic anhydride at 300 or 540 μg/m^3 on day 22 or day 29, respectively. In the 500 μg/m^3 exposure group, anti-trimellitic anhydride–rat serum albumin IgM and IgA began increasing on day 5 and peaked on day 20. IgG antibodies began increasing on day 7 and also peaked on day 20. These rats had a mean of 216 haemorrhagic lung foci. Rats of the low exposure group (330 μg/m^3) that were not rechallenged had fewer lung foci than the rechallenged rats. The rechallenged rats also demonstrated a strong correlation between antibody measures and lung injury. A subgroup of rats was exposed to 500 μg/m^3 on days 1 and 5 and challenged on day 29 with the same concentration. This subgroup had a mean of 112 haemorrhagic lung foci. A good correlation between antibody response and lung injury was observed.

Zhang et al. (2006) exposed Brown Norway rats to trimellitic anhydride aerosol at concentrations of 0.04, 0.4, 4, or 40 mg/m^3 for 10 min, once per week, for over 10 weeks. The rats were then challenged with trimellitic anhydride aerosol at 40 mg/m^3. Rats sensitized in the 40 mg/m^3 group developed specific IgE and both early-phase and late-phase airway responses. Rats in the 4 mg/m^3 group exhibited a lower but stable specific IgE response; early-phase and late-phase airway responses were observed only after the 40 mg/m^3 challenge and were greater than those observed in the 40 mg/m^3 sensitization group. Histopathological changes were exposure dependent and included eosinophilic granulomatous interstitial pneumonia, perivascular eosinophil infiltrates, bronchial-associated lymphoid tissue hyperplasia, and peribronchiolar plasma cell infiltrates.

Dykewicz et al. (1988) sensitized two rhesus monkeys intrabronchially with serum from a human worker who had trimellitic anhydride asthma and high titres of anti-trimellitic anhydride–human serum albumin IgE, IgG, and IgA. The monkeys were challenged with trimellitic anhydride–human serum albumin aerosol and developed bronchospasm. After 1 week, the challenge was negative. Passive cutaneous anaphylaxis (using the Prausnitz-Küstner test) was positive.

Hatanaka et al. (1997) sensitized rabbits subcutaneously to phthalic anhydride–rat serum albumin. Anti-phthalic anhydride–rat serum albumin IgG was observed in high titres, as were anti-phthalic anhydride–human serum albumin IgG and anti-human serum albumin IgG. The anti-phthalic anhydride–human serum albumin antibodies were cross-reactive with hexahydrophthalic anhydride–human serum albumin, methyl hexahydrophthalic anhydride–human serum albumin, and methyl tetrahydrophthalic anhydride–human serum albumin.

Hayes et al. (1992a) developed a guinea-pig model for trimellitic anhydride–induced airway hypersensitivity. Guinea-pigs were sensitized intradermally with 0.1 ml of 0.3% trimellitic anhydride in corn oil. Specific serum IgG_1 antibody levels were increased in all sensitized animals. IgE antibodies were detected in six out of eight sensitized animals. On days 21–28, guinea-pigs were challenged with a tracheal dose of 50 μl of 1% trimellitic anhydride–guinea-pig serum albumin, which caused increased lung resistance in sensitized animals compared with non-sensitized animals. Evans blue testing revealed airway microvascular leakage in sensitized guinea-pigs. Challenge by nose inhalation of trimellitic anhydride at 12 000 μg/m^3 for 30 min resulted in a significant increase in bronchial reactivity at 8 h post-exposure, which was accompanied by an eosinophilic inflammatory exudate.

Arakawa et al. (1993b) sensitized guinea-pigs by two intradermal injections of 0.1 ml of 0.3% trimellitic anhydride in corn oil and evaluated the time course of immune and airway responses. Animals were challenged with 50 μl of 0.5% trimellitic anhydride–guinea-pig serum albumin at 1, 2, 3, 5, and 8 weeks post-sensitization. The challenge induced significant increases in lung resistance, which reached a maximum at 2.5 min in the 1-week group and between 5 and 6 min in the other groups. Significant extravasation was observed, which increased up to 8 weeks. Specific IgG_1 antibodies were detected in all guinea-pigs of the 3-, 5-, and 8-week groups, which correlated with extravasation but not with increased lung resistance.

Zhang et al. (1998b) found specific IgE and IgG antibodies induced in intradermal studies of phthalic anhydride, trimellitic anhydride, maleic anhydride, hexahydrophthalic anhydride, methyl hexahydrophthalic anhydride, and methyl tetrahydrophthalic anhydride.

Cui et al. (1997) sensitized Brown Norway rats intradermally with trimellitic anhydride and then challenged the rats either once or 7 times with trimellitic

anhydride–rat serum albumin. Anti-trimellitic anhydride IgE and IgG were observed at high levels in all sensitized rats compared with controls. Repeated challenges with allergen, but not single challenges, caused significant bronchial hyperreactivity in sensitized rats. For example, repeated low-dose challenges produced greater hyperreactivity than a single 10-fold higher dose. Sensitized and single-challenged rats exhibited bronchial eosinophilia, although the non-sensitized non-challenged and sensitized rechallenged rats did not.

Arts et al. (1998) challenged intradermally sensitized Brown Norway rats with trimellitic anhydride by inhalation, which induced immediate bronchoconstriction. Sensitized rats also exhibited eosinophilic aggregates, goblet cell hyperplasia and hypertrophy in the lungs, and the induction of haemorrhages. Non-sensitized rats exhibited less marked eosinophilic infiltration of the lungs after challenge tests.

Arts et al. (2004) investigated airway responses of sensitized Brown Norway and Wistar rats to trimellitic anhydride. Rats were sensitized by dermal applications of 50% weight by volume (w/v) and then 25% w/v trimellitic anhydride. All rats were challenged 3 weeks after the first sensitization to a range of trimellitic anhydride concentrations (0.2–61 mg/m^3 for Brown Norway rats; 15–250 mg/m^3 for Wistar rats). Sensitized Brown Norway rats displayed elevated total IgE levels; inhalation challenge with ≥2 mg/m^3 caused laryngeal inflammation with squamous epithelial metaplasia and pulmonary haemorrhages. Decreased breathing frequency and altered breathing patterns were concentration related. Inhalation challenges with ≥12 mg/m^3 caused increased lung weight. Nonspecific airway responsiveness was increased at 46 and 61 mg/m^3. The non-sensitized Brown Norway rats displayed laryngeal squamous metaplasia (at higher challenge concentrations), decreased breathing frequency, and a breathing pattern characteristic of irritation. Sensitized Wistar rats exhibited airway inflammation and pulmonary haemorrhages upon challenge, but no functional changes, even at the highest concentrations that cause irritation. The authors concluded that the lowest NOEL was 0.2 mg/m^3.

Pauluhn (2003) performed a dose–response analysis and time course evaluation for intradermally sensitized Brown Norway rats challenged by inhalation. Sensitization was performed using 1, 5, or 25% trimellitic anhydride in acetone/olive oil that was applied 2 times, 1 week apart. Inhalation challenges were performed at 25–30 mg trimellitic anhydride/m^3 for 30 min on days 17, 24, 41, 47, 55, and 66. Breathing patterns were altered only in the rats sensitized with 5% or 25% trimellitic anhydride. These rats also demonstrated an increased responsiveness to methacholine aerosol challenge the day following trimellitic anhydride challenge (only on day 17). The concentration of 5% trimellitic anhydride was determined to be the minimal sensitizing concentration. A time-related increase in airway responsiveness was observed. After the last challenge (day 66), the respiratory response and lung weights were similar to those observed in the repetitively rechallenged control group (non-sensitized intradermally).

Zhang et al. (1997, 1998a) developed a protocol for the intradermal sensitization of guinea-pigs to hexahydrophthalic anhydride in order to study the mechanism of allergy. Guinea-pigs were immunized by single and booster intradermal injections of 0.1 ml of 0.02, 0.1, 0.5, 5, and 10% mixtures of hexahydrophthalic anhydride in olive oil. Single injections of <0.5% did not cause production of specific IgE or IgG antibodies. A single injection of the 5% mixture induced optimal levels of IgG after 14 days. Injections of 0.5–10% hexahydrophthalic anhydride produced low IgE titres and were positive in only 40–50% of the animals. IgE induction was achieved only by booster injections (Zhang, 1997). Allergen challenge in hexahydrophthalic anhydride–sensitized guinea-pigs caused airway obstruction and plasma extravasation responses that were related to serum levels of specific IgG_1 (Zhang et al., 1997, 1998a).

Guinea-pigs sensitized to hexahydrophthalic anhydride or methyl tetrahydrophthalic anhydride and challenged via inhalation or intravenous injection with the corresponding guinea-pig serum albumin conjugate developed anaphylactic bronchoconstriction (Zhao et al., 1997). The critical dose was determined to be 40 µg/kg bw.

Dearman & Kimber (1991) developed a mouse model to differentiate chemicals for different types of allergenicity. Mice were topically sensitized by application of the test chemical in 4:1 acetone:olive oil to a shaved flank under an occluded patch for 48 h. Ear thickness was measured after 5 days, and the dorsum of both ears was treated with 25 µl of the test chemicals, trimellitic anhydride and 2,4-dinitrochlorobenzene. 2,4-Dinitrochlorobenzene is a potent contact allergen that lacks respiratory sensitization properties. Trimellitic anhydride and 2,4-dinitrochlorobenzene induced comparable levels of contact sensitization and antihapten IgG. However, only trimellitic anhydride induced IgE production. In addition, trimellitic anhydride induced IgG_{2b} rather than IgG_{2a}, whereas the opposite was observed for 2,4-dinitrochlorobenzene. This may have been due to differences in T lymphocyte responses to the chemicals (Th_1 versus Th_2). Similar responses have been observed with phthalic anhydride, maleic anhydride, hexahydrophthalic anhydride, and methyl tetrahydrophthalic anhydride (Dearman & Kimber, 1992; Dearman et al., 2000). Arts et al. (1997) conducted similar experiments in Brown Norway rats using trimellitic

anhydride, dinitrochlorobenzene, formaldehyde, and methyl salicylate. A significant increase in serum IgE was observed after trimellitic anhydride exposure, but not after exposure to the other chemicals.

8.8 Mode of action

Cyclic acid anhydrides are irritants of the skin and mucous membranes of the eyes and respiratory organs. This is due to rapid reactions with water, which form the corresponding acids responsible for the irritation.

Experiments with sensitized animals have demonstrated the formation of anhydride-specific IgE and IgG antibodies. As described above (section 8.7), phthalic anhydride, trimellitic anhydride, and hexahydrophthalic anhydride challenges to sensitized animals resulted in obstructive bronchial reactions.

Animal studies using blocking agents have demonstrated that histamine and thromboxane A_2 are primarily responsible for the early and late bronchoconstriction responses to trimellitic anhydride (Hayes et al., 1992b, 1995; Arakawa et al., 1993a, 1994b). Leukotrienes and histamine were found to mediate airway exudation. Pretreatment of sensitized guinea-pigs with budesonide, an anti-inflammatory corticosteroid, significantly inhibited the increase in airway responsiveness, but not the eosinophilic inflammation caused by exposure to trimellitic anhydride dust (Hayes et al., 1993). Rats pretreated with cyclophosphamide, an immunosuppressant, did not develop lung lesions or antibody responses after exposure to trimellitic anhydride at 95 $\mu g/m^3$, 6 h/day, 5 days/week, for 2 weeks (Leach et al., 1988). This study demonstrated that elimination of T and B lymphocyte function could prevent trimellitic anhydride–induced lesions. Pretreatment of guinea-pigs with cyclosporin A caused inhibition of trimellitic anhydride–induced immunization processes; betamethasone and azelastine did not cause inhibition (Arakawa et al., 1994a). However, a study by Pullerits et al. (1997) in Brown Norway rats demonstrated that both betamethasone and cyclosporin A administered during the sensitization period inhibited development of trimellitic anhydride–specific IgE and IgG.

Yan et al. (1995) demonstrated that sensitized guinea-pigs underwent activation of inducible nitric oxide synthase in bronchial tissue after challenge with trimellitic anhydride–guinea-pig serum albumin.

Fraser et al. (1995) pretreated guinea-pigs with cobra venom, which reduced complement component C_3 in bronchoalveolar lavage fluid after challenge with trimellitic anhydride–guinea-pig serum albumin. Cobra venom pretreatment did not affect immediate bronchoconstriction and microvascular leakage. However, cobra venom pretreatment significantly reduced trimellitic anhydride–induced increases in mononuclear cells, total white blood cells and red blood cells, and erythrocyte peroxidase activity. These results indicated that inhibition of complement activation by cobra venom prevented inflammatory cell infiltration in trimellitic anhydride–induced asthma.

Larsen et al. (2001) also investigated the role of the complement system in trimellitic anhydride–induced allergic response in guinea-pig lung. Guinea-pigs were sensitized by intradermal injection of trimellitic anhydride. The complement activation product C_{3a} was detected in bronchoalveolar lavage of both sensitized and non-sensitized guinea-pigs after intratracheal challenge with trimellitic anhydride–guinea-pig serum albumin. In sensitized animals, this challenge caused significant increases in eosinophils, neutrophils, and macrophages in lung and increases in red blood cells and protein in airspace. In a follow-up study, Larsen & Regal (2002) used 1 mg trimellitic anhydride dust for the challenge rather than trimellitic anhydride conjugated to guinea-pig serum albumin. The dust challenge was delivered by intratracheal insufflation. The non-sensitized guinea-pigs displayed significant increases in pulmonary resistance and decreases in dynamic lung compliance and blood pressure after challenge. The sensitized animals displayed significantly greater effects compared with the non-sensitized animals. In both sensitized and non-sensitized guinea-pigs, the dust challenge caused increased eosinophils in the lung tissues. This study demonstrates that trimellitic anhydride dust causes significant airway obstruction and eosinophilia in non-sensitized animals, and even greater effects in sensitized animals.

Valstar et al. (2006a) investigated the role of alveolar macrophages in asthma-like symptoms caused by trimellitic anhydride. Female Brown Norway rats were sensitized by dermal application of trimellitic anhydride on days 0 and 7. The day prior (day 20) to inhalation challenge with trimellitic anhydride (day 21), the rats were treated intratracheally with either empty liposomes (sham control) or liposomes containing clodronate (dichloromethylene diphosphonate) to deplete the lungs of alveolar macrophages. The sensitized rats exhibited decreased lung function parameters during and within 1 h after challenge compared with non-sensitized rats. Depletion of alveolar macrophages alleviated the trimellitic anhydride–induced decrease in lung function parameters and caused a quicker recovery compared with the sham controls; however, trimellitic anhydride–induced tissue damage and inflammation 24 h after challenge were augmented. This study concluded that alveolar macrophages have a dual role, since they potentiate the immediate decrease in lung function but suppress the inflammatory reaction 24 h later. Valstar et al. (2006b) conducted the same study but performed the inhalation challenge with trimellitic anhydride–bovine

serum albumin. This caused an early asthmatic response in the sensitized rats compared with the non-sensitized rats, irrespective of alveolar macrophage depletion. In addition, the challenge induced airway inflammation and tissue damage only when alveolar macrophages were depleted, irrespective of sensitization. These data indicate that alveolar macrophages inhibit nonspecific damage and inflammatory cell influx into the lungs caused by trimellitic anhydride–bovine serum albumin challenge.

Regal et al. (2001) evaluated eosinophil infiltration into lungs of BALB/c mice sensitized intradermally with 0.1 ml of either 3% trimellitic anhydride or 0.3% ovalbumin (positive control). These mice were challenged 3 weeks later with 30 or 400 µg trimellitic anhydride–mouse serum albumin or 30 µg ovalbumin by intratracheal instillation. The numbers of eosinophils and neutrophils in bronchoalveolar lavage fluid were determined by eosinophil peroxidase and myeloperoxidase activity, respectively. In the trimellitic anhydride–sensitized mice, the trimellitic anhydride–mouse serum albumin challenge resulted in a significant increase in eosinophil peroxidase activity. A small, but significant, increase was also observed in the non-sensitized mice. Total IgE in plasma and bronchoalveolar lavage fluid was significantly higher in trimellitic anhydride–sensitized mice than in the non-sensitized mice. The magnitudes of these responses were similar to those elicited by ovalbumin sensitization and challenge.

9. EFFECTS ON HUMANS

In humans, cyclic acid anhydrides can cause irritation and sensitization after direct contact with the skin and the mucous membranes or after exposure by inhalation (Zeiss et al., 1999). The irritative symptoms (itching, lacrimation, sneezing, rhinorrhoea, cough, and dyspnoea) begin immediately following exposure to high concentrations of dusts or vapours. The most common allergic diseases are rhinoconjunctivitis and asthma, both immediate-type IgE-mediated allergies. Also, late-type respiratory symptoms with specific IgG antibodies have been described. Less frequent consequences are the severe disease called pulmonary disease–anaemia syndrome, contact eczema, contact urticaria, allergic laryngitis, and allergic alveolitis.

9.1 Irritation and sensitization

Conjunctival, nasal, and bronchial irritation are common immediate features following exposure to acid anhydrides (Baader, 1955; Menschick, 1955; Zeiss et al., 1977; Nielsen et al., 1988, 1994a). On mucous membranes and on sweating skin, they are hydrated to acids and cause irritation, reddening, corneal damage, caustic dermatitis, and burns (Menschick, 1955; Malten & Zeilhuis, 1964).

The human nasal irritation threshold for phthalic anhydride has been reported to be 30 000 µg/m^3 and that for maleic anhydride 5480 µg/m^3, but exposure duration, generation of particles, and particle sizes were not reported (Ruth, 1986).

Irritant haemorrhagic rhinitis has been reported as a result of maleic anhydride exposure (Baur et al., 1995).

9.2 Effects of repeated exposure

Allergic reactions of the skin and conjunctiva and allergic respiratory manifestations are well known effects of occupational exposure to cyclic acid anhydrides. Respiratory diseases include occupational allergic rhinoconjunctivitis and occupational asthma. Urticaria and allergic rhinoconjunctivitis often precede asthma. Cases of haemorrhagic alveolitis, haemorrhagic anaemia, allergic alveolitis, and allergic laryngitis have also been reported in association with exposure to anhydrides.

9.2.1 Allergic dermatitis

Allergic contact dermatitis due to cyclic acid anhydrides is rare. There are only two case-reports on delayed-type contact allergy. In one report, a laboratory technician was sensitized by dodecenylsuccinic anhydride. The delayed-type allergic reaction was verified with positive patch tests. Tests on 15 controls were negative (Goransson, 1977). In the other, a worker contracted allergic contact dermatitis when exposed to methyl hexahydrophthalic anhydride. Patch test reactions followed an exposure–response pattern. Immunohistochemical and electron microscopic observations indicated that the patch test reactions were conventional delayed allergic reactions. The patient also had an immediate-type contact dermatitis verified by positive skin prick tests and the presence of IgE antibodies (Kanerva et al., 1997).

One case-report described the presentation of a 33-year-old woman with a 2-month history of an intermittent itchy rash on the neck and around the eyes, associated with eyelid swelling (Moffitt & Sansom, 2002). Patch tests revealed a positive reaction to a phthalic anhydride/trimellitic anhydride/glycols copolymer (1%) ingredient present in nail varnish. She also had positive test reactions to five colouring bases that contained this ingredient. She had negative reactions to tosylamide/formaldehyde resin, which is typically the culprit for cosmetic-induced allergic contact dermatitis. Twelve treated controls were negative.

Patch tests were administered to 190 workers at five ceramics factories. The patch test series included maleic anhydride and phthalic anhydride. Two workers had a positive patch test reaction to maleic anhydride; the authors reported that three workers earlier had skin sensitization from maleic anhydride (Motolese et al., 1993).

IgE-mediated contact urticaria is known to be induced by contact or even airborne exposure to cyclic anhydrides.

Urticarial reactions have been reported among workers in phthalic anhydride production (Baader, 1955; Menschick, 1955). There are a few case-reports of immediate-type dermatitis due to acid anhydrides. Jolanki et al. (1987) reported on a case of methyl hexahydrophthalic anhydride–induced contact urticaria in a worker in a factory where electronic components were filled with methyl hexahydrophthalic anhydride–cured epoxy resin.

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

Kanerva et al. (1999) reported a case of airborne contact urticaria in a worker in the electronics industry due to methyl hexahydrophthalic anhydride and hexahydrophthalic anhydride exposure.

A welder exposed to welding fumes of chlorinated polyester paint containing chlorendic anhydride developed contact urticaria. An IgE-mediated allergy was verified with skin prick tests and specific IgE antibodies. An open test with chlorendic anhydride was also positive (Keskinen et al., 2000).

An operator in a firm manufacturing polyester resin developed urticaria following exposure to maleic anhydride dust (Kanerva & Alanko, 2000).

9.2.2 Respiratory allergies

A number of occupational cases of asthma or rhinoconjunctivitis due to exposure to different cyclic acid anhydrides have been reported. The symptoms are those of typical occupational asthma and rhinitis. After a symptom-free latency period, the worker experiences symptoms when exposed. The diagnosis has been based on the exposure, symptoms, and a cause–effect relationship proven with immunological tests or challenge tests.

The proof of IgE mediation in immediate-type asthma or rhinitis due to acid anhydrides is convincing. Specific IgE to several acid anhydrides—phthalic anhydride, trimellitic anhydride, maleic anhydride, tetrachlorophthalic anhydride, hexahydrophthalic anhydride, tetrachlorophthalic anhydride, hexahydrophthalic anhydride, himic anhydride, methyl hexahydrophthalic anhydride, methyl tetrahydrophthalic anhydride, and chlorendic anhydride—has been found (Maccia et al., 1976; Sale et al., 1981; Zeiss et al., 1982; Howe et al., 1983; Moller et al., 1985; Topping et al., 1986; Rosenman et al., 1987; Nielsen et al., 1988, 1992; Welinder et al., 1990, 1994, 2001; Liss et al., 1993; Drexler et al., 1994; Yokota et al., 1997).

The induction time for positive specific IgE antibodies was 8.8 months (range 1–35 months) when workers exposed to hexahydrophthalic anhydride, methyl hexahydrophthalic anhydride, and methyl tetrahydrophthalic anhydride were followed. Inhibition studies and passive transfer studies have supported the specificity of IgE antibodies, but cross-reactivity among some acid anhydrides has been reported (Topping et al., 1986; Welinder & Nielsen, 1991; Drexler et al., 1994; Lowenthal et al., 1994).

Specific IgG antibodies have been studied especially in connection with sensitization to trimellitic anhydride. Specific IgG antibodies against trimellitic anhydride–human serum albumin have been correlated with late-onset occupational asthma due to trimellitic anhydride (Patterson et al., 1978, 1979, 1982; Turner et al., 1980; Sale et al., 1981). No cross-reactivity with phthalic anhydride, maleic anhydride, hexahydrophthalic anhydride, or tetrachlorophthalic anhydride was found when the specificity of IgG antibodies against trimellitic anhydride–human serum albumin conjugate was investigated (Gerhardsson et al., 1993).

9.2.2.1 Phthalic anhydride

Wernfors et al. (1986) conducted a cross-sectional study of 48 current and 70 former workers in four plants producing alkyd or unsaturated polyester resins. The phthalic anhydride dust concentrations during the loading of the reactors and handling of bags ranged up to 13 000 µg/m^3. The 8-h time-weighted average was approximately 400 µg/m^3. The fraction of respirable dust was about 40%. Twenty-eight workers (24%) had work-related rhinitis, 21 (18%) had asthma, and 13 (11%) had symptoms of chronic bronchitis. The length of exposure ranged from 2 months to 40 years. In 10 of the 21 asthmatics, rhinitis preceded the asthmatic symptoms. The latency period before onset of the respiratory symptoms ranged from 1 month to 16 years. A positive

skin scratch test was found in 3 of the 11 asthmatics, but none of the non-asthmatics.

In a survey of workers who produced alkyd or unsaturated polyester resins, Nielsen et al. (1988) found that 46% of those in the high exposure group (phthalic anhydride concentrations of 1500–17 400 μg/m^3) had conjunctivitis, 40% had rhinitis, and 14% had asthma. In the low exposure group (<100 μg/m^3), the corresponding figures were 20% for conjunctivitis and rhinitis and 0% for asthma. There was no association between specific IgE antibodies and phthalic anhydride exposure.

In a study of phthalic anhydride–exposed workers, sensitization was found to be uncommon at the low exposure levels measured, 8.9–11.9 μg/m^3 (Barker et al., 1998).

9.2.2.2 Trimellitic anhydride

Letz et al. (1987) examined all nine workers at a barrel manufacturing plant who were exposed to trimellitic anhydride breathing zone concentrations of 1700–3600 μg/m^3. Four workers had trimellitic anhydride–induced irritant effects. Three had symptoms and IgG levels consistent with late-type respiratory syndrome, one had specific IgE against trimellitic anhydride, and one worker was asymptomatic.

No trimellitic anhydride–related disease was found over a 2-year period among 11 factory workers preparing epoxy resin coating material. The trimellitic anhydride exposure level was less than 180 μg/m^3 (McGrath et al., 1984).

Zeiss et al. (1990) conducted a 12-year (1976–1987) clinical and immunological study of 196 workers in the trimellitic anhydride manufacturing industry. The workers were administered a questionnaire and tests for total trimellitic anhydride antibodies and trimellitic anhydride–specific IgE. IgE-mediated immediate-type asthma or rhinitis was found in 21 workers and late-type asthma in 10 workers. A total of 113 workers had only irritant symptoms, and 46 were asymptomatic. No data were available on exposure, but there was an annual decline in the number of sensitized workers due to improvements in the workplace.

In 1988–1989, Zeiss et al. (1992) conducted a cross-sectional study of 474 workers in the same factory as in his earlier (1990) study. Five exposure groups were assigned by an industrial hygienist on the basis of job history and the results of personal monitoring. Trimellitic anhydride–specific IgE antibodies were found only in the high exposure group (0.54–6500 μg/m^3, geometric mean = 170 μg/m^3). Sensitizations and illnesses due to trimellitic anhydride were concentrated in the three highest exposure groups (170 μg/m^3 [geometric mean]; 87 μg/m^3 [geometric mean]; and 0.44–0.55 μg/m^3). Current or former smoking, but not age, sex, or date of hire, was found to be associated with total antibody levels (P = 0.01). One year after 29 sensitized workers were moved to low-exposure jobs, their symptoms and pulmonary functions had improved and their specific antibody levels had decreased (Grammer et al., 1993).

Barker et al. (1998) examined 63 workers exposed to trimellitic anhydride. The prevalence of sensitization and work-related symptoms increased with increasing exposure. The odds ratios for positive skin prick tests for workers exposed to 10–40 μg/m^3 and >40 μg/m^3 compared with workers exposed to <10 μg/m^3 were 10.0 and 20.7, respectively. The odds ratios of work-related respiratory symptoms in those exposed to 10–40 μg/m^3 and >40 μg/m^3 were 5.9 and 7.4, respectively. There was no increase in prevalence of sensitization or symptoms with smoking or atopy.

9.2.2.3 Hexahydrophthalic anhydride

Moller et al. (1985) reported on 27 workers exposed to hexahydrophthalic anhydride from epoxy resin moulding. Eleven workers were reported to be exposed to an average of 3800 μg/m^3 (range 1300–8200 μg/m^3); 16 workers were reported to be exposed to 1900 μg/m^3 (range 600–3100 μg/m^3). Of the 11 in the high exposure group, 1 had asthma and 9 had rhinitis/conjunctivitis. Of those in the low exposure group, 4 had asthma and 13 had rhinitis/conjunctivitis.

Grammer & Shaughnessy (1996) followed 28 employees with hexahydrophthalic anhydride–induced asthma or rhinitis for at least 1 year after removal from exposure. The symptoms and spirometry normalized in all but one worker. There was a decline in the hexahydrophthalic anhydride–specific IgE in 25 workers.

A rare case of specific hexahydrophthalic anhydride–induced laryngitis was reported in an electrician. A skin prick test was positive, and specific IgE antibodies to the conjugate were found. The laryngeal reaction was verified by a challenge test (Sala et al., 1996).

9.2.2.4 Hexahydrophthalic anhydride and methyl hexahydrophthalic anhydride

Welinder et al. (1994) found that workers exposed to hexahydrophthalic anhydride and methyl hexahydrophthalic anhydride at levels of <10, 10–50, and >50 μg/m^3 had specific IgE antibodies, but there was no evidence of a dose–response.

Welinder et al. (2001) followed workers exposed to hexahydrophthalic anhydride and methyl hexahydro-

phthalic anhydride for an average of 33 months (range 1–85 months) and found that 27% had been sensitized and had specific IgE antibodies. Another 21% had positive reactions in skin prick tests with corresponding hexahydrophthalic anhydride conjugates. The mean exposure level was reported to be 38.7 μg/m^3 (range 1–187 μg/m^3). An effect was found between atopy and specific IgE antibodies; the effect of smoking was not significant.

Nielsen et al. (2001) evaluated the exposure–response relationships for hexahydrophthalic anhydride and methyl hexahydrophthalic anhydride and the development of specific IgE and IgG antibodies and work-related symptoms. There were 154 exposed workers and 57 referents in this study of an epoxy resin–using factory. Air levels of these anhydrides were determined by GC-MS. The air levels ranged from <1 to 94 μg/m^3 for hexahydrophthalic anhydride and from <3 to 77 μg/m^3 for methyl hexahydrophthalic anhydride. For the exposed workers, there were high prevalences of sensitization (IgE, 22%; IgG, 21%), which correlated with exposure. Atopy and smoking did not increase this risk. Work-related symptoms, such as eye irritation, nose irritation, nose bleeding, and lower airways irritation, were also more prevalent among the workers compared with the referents.

9.2.2.5 Methyl tetrahydrophthalic anhydride

Nielsen et al. (1992, 1994b) found a higher prevalence of asthma and work-related symptoms of the eyes, nose, and pharynx among 140 current and 26 former workers who used methyl tetrahydrophthalic anhydride epoxy curing agent compared with 33 controls. The prevalence of asthma among the current and former workers was 11% versus 0% in the controls. Symptoms of the eyes, nose, and pharynx among the current and former workers compared with controls were 31% versus 0%, 53% versus 9%, and 26% versus 6%, respectively. The percentages of current and former workers with positive skin prick tests, specific IgE antibodies, and specific IgG antibodies were 16%, 18%, and 12%, respectively; the tests among the controls were all negative. There were statistically significant exposure–response relationships between the exposure symptoms of the eyes and upper airways, dry cough, positive skin prick tests, and specific IgE and IgG antibodies. The concentration of methyl tetrahydrophthalic anhydride was under 150 μg/m^3. No association between sensitization and either atopy or smoking was found.

Yokota et al. (1996) conducted a study of 28 workers at two plants where methyl tetrahydrophthalic anhydride was used as a hardener in epoxy resin insulation. Air concentrations were reported to be between 1.09 and 22.4 μg/m^3. Specific IgE antibodies were detected in nine (32%) of the workers, eight of whom had nasal symptoms. Total IgE levels were significantly higher in the group with specific IgE.

A larger study of the same population found that among 148 workers, 66% had specific IgE antibodies (Yokota et al., 1997). The authors found that the relative risk for elevated methyl tetrahydrophthalic anhydride–specific IgE among smokers was 4.1.

In a study of the exposure–response relationship, Yokota et al. (1999) found that the minimal level for an association between methyl tetrahydrophthalic anhydride exposure and work-related symptoms was 15–22 μg/m^3.

In a study of workers exposed to average methyl tetrahydrophthalic anhydride concentrations of 10.1 μg/m^3 (range 9–38 μg/m^3) and 5.9 μg/m^3 (range 0–50 μg/m^3), the percentages positive for specific IgE antibodies were 8.6% and 8.9% and for positive skin prick tests 4.2% and 2.2%, respectively (Welinder et al., 2001). The observation times for the two exposure groups were 26 months (range 2–38 months) and 40 months (range 1–105 months). There was no evidence of a dose–response with respect to peak exposure levels.

Drexler et al. (1994, 1999) examined 110 workers exposed to methyl tetrahydrophthalic anhydride and hexahydrophthalic anhydride and found that 20 of them were sensitized according to skin prick tests and specific IgE determination. Occupational asthma or rhinitis was verified for six cases. The concentration of anhydrides in the air was not measured until 1995 (<0.5–36 μg/m^3).

9.2.2.6 Tetrachlorophthalic anhydride

Seven cases of occupational asthma were reported at a factory that made electronic components and used tetrachlorophthalic anhydride as an epoxy resin curing agent. Inhalation challenge tests confirmed the diagnoses. Specific skin prick tests were positive, and specific IgE antibodies against tetrachlorophthalic anhydride–human serum albumin were detected (Venables et al., 1987; Barker et al., 1998).

Tetrachlorophthalic anhydride was found to interact with atopy in the production of specific IgE antibodies (Venables et al., 1985).

Four patients with asthma caused by occupational exposure to tetrachlorophthalic anhydride had dust challenge tests that used eight different levels of tetrachlorophthalic anhydride exposure. Significant reductions in forced expiratory volume were found to be associated with exposures ranging from 4.1 to 66.7 μg/m^3 (Venables & Newman Taylor, 1990).

Liss et al. (1993) found the prevalence of work-related respiratory symptoms to be 27% (wheeze), 29% (shortness of breath), and 39% (chest tightness) in a study of 52 workers in a factory using tetrachlorophthalic anhydride–cured epoxy resin. Occupational asthma was reported to be present in 35% of the workers, according to questionnaire results. Thirty-one per cent of the workers had specific IgE and 39% had specific IgG against tetrachlorophthalic anhydride–human serum albumin. The mean tetrachlorophthalic anhydride concentration was between 210 and 390 $\mu g/m^3$. The prevalence of specific IgE was highest among those with the highest exposure. Installation of ventilation controls at the facility decreased the exposure by an order of magnitude from a range of 140–590 $\mu g/m^3$. Following the installation of the ventilation controls, there was a marked decrease in symptoms, and there were no new cases of occupational asthma.

9.2.2.7 Pyromellitic dianhydride

Meadway (1980) reported two cases of asthma from exposure to pyromellitic dianhydride–cured epoxy resin. Challenge tests were positive for both workers.

Baur et al. (1995) conducted a cross-sectional study of 92 workers who had primary exposure to pyromellitic dianhydride as well as to phthalic anhydride, maleic anhydride, and trimellitic anhydride. Of those with less than 1 year of exposure, 56 had work-related symptoms. Eighteen had dyspnoea, and eight had bronchial obstruction. Specific IgE antibodies were found in 15 workers; 12 of those had symptoms. Eleven cases of haemorrhagic rhinitis were found in workers with more than 15 years of exposure. Only one of the cases had specific IgE exposure. The symptoms were reversible in workers whose exposure stopped after a work period of about 8–9 months.

Czuppon et al. (1994) reported a case of acute haemorrhagic alveolitis associated with anaemia in a patient exposed to pyromellitic dianhydride.

9.2.2.8 Other anhydrides

A worker in maleic anhydride production who previously had maleic anhydride–related asthmatic symptoms developed severe haemolytic anaemia. He relapsed 2 weeks after returning to work the following year. Afterward, he remained stable if he avoided maleic anhydride exposure. He had a high titre of maleic anhydride–specific IgE but not IgG antibodies (Gannon et al., 1992; Jackson & Jones, 1993).

In a study of maleic anhydride–exposed workers, sensitization was found to be uncommon at the low exposure levels measured, 1.8–2.8 $\mu g/m^3$ (Barker et al., 1998).

A worker exposed to himic anhydride powder in the manufacture of a flame retardant developed rhinitis, hives, and wheezing after 1 year of employment. Of the 20 workers who were tested at the plant, 3 of the 6 symptomatic workers had specific IgE antibodies for himic anhydride–human serum albumin conjugate (Rosenman et al., 1987).

A welder developed work-related urticaria and asthmatic symptoms from cyclic acid anhydrides used as a hardener. A skin prick test with cyclic acid anhydrides–human serum albumin conjugate was positive, as was an open test for urticaria. Specific IgE antibodies were also detected (Keskinen et al., 2000).

9.2.3 *Other effects*

Riboli et al. (1983) conducted a lung cancer case–control study in a town in Italy where a chemical plant that produced mainly acetylene, phthalic anhydride, and their derivatives was located. Other exposures at the chemical plant included phthalates and soot. The cases were males in the town who had died from lung cancer during the period 1976–1979. The controls were males from the same town who had died from diseases other than lung cancer during the same period. After controlling for age and smoking, the odds ratio for lung cancer for having worked at the chemical plant relative to those never occupationally exposed was 5.6 (95% confidence interval [CI] = 1.9–16.2). The risk for exposure to lung carcinogens in work environments other than the chemical plant was 1.7 (95% CI = 0.9–3.5).

There are no studies evaluating reproductive or genotoxic effects in humans.

9.3 Mode of action in humans

Phthalic anhydride has been classified as a moderate sensitizer that causes allergic contact dermatitis of type IV (Gad, 1988). More recent studies using cytokine stimulation concluded that phthalic anhydride, trimellitic anhydride, maleic anhydride, hexahydrophthalic anhydride, and methyl tetrahydrophthalic anhydride were not contact allergens (Dearman & Kimber, 1991, 1992; Dearman et al., 2000). Case-reports in humans of allergic contact dermatitis are limited, suggesting that the potency of cyclic acid anhydrides is low (Kanerva et al., 1997; Kanerva & Alanko, 2000).

Cyclic acid anhydrides have been observed to cause IgE-mediated contact urticaria in humans. For example, methyl hexahydrophthalic anhydride, methyl tetrahydrophthalic anhydride, hexahydrophthalic anhydride, chlorendic anhydride, and maleic anhydride have induced contact urticaria in exposed workers (Jolanki et al., 1987; Tarvainen et al., 1995; Kanerva et al., 1999; Kanerva & Alanko, 2000; Keskinen et al., 2000). There

are some reports of contact urticaria via airborne exposure without skin contact (Tarvainen et al., 1995; Kanerva et al., 1999).

Allergic asthma is a well documented disease of cyclic acid anhydride exposure in workers. Allergic asthma is often preceded by rhinoconjunctivitis. IgE-mediated sensitization has been verified in exposed workers using skin prick tests with conjugates of the cyclic acid anhydrides and human serum albumin. Bronchial hyperresponsiveness has been correlated with specific sensitization (Barker et al., 2000).

The formation of protein adducts is hypothesized to be the first step in sensitization. This has been demonstrated by total protein and albumin adducts of hexahydrophthalic anhydride and methyl hexahydrophthalic anhydride in the plasma of exposed workers (Rosqvist et al., 2000).

Flaherty et al. (1988) demonstrated mediator release during cyclic acid anhydride sensitivity. Basophilic leukocytes challenged in vitro with phthalic anhydride or tetrachlorophthalic anhydride–human serum albumin conjugates resulted in a release of histamine.

Humans exposed to fumes from trimellitic anhydride–cured epoxy resin have been reported to exhibit pulmonary disease–anaemia syndrome, a rare disease with haemorrhagic alveolitis and specific IgG antibodies. Animal studies have demonstrated similar reactions (Chandler et al., 1987; Leach et al., 1987).

10. EVALUATION OF HEALTH EFFECTS

10.1 Hazard identification and dose–response assessment

The most common symptom from exposure to cyclic acid anhydrides is irritation of the mucous membranes.

Many of the anhydrides are known to induce IgE-mediated sensitization followed by allergic disease (e.g. allergic rhinitis often associated with allergic conjunctivitis and bronchial asthma).

Allergic skin diseases caused by acid anhydrides include IgE-mediated contact urticaria. Such cases are rare, however. Even more rare are cases of allergic contact dermatitis.

There is no evidence of a carcinogenic effect of cyclic acid anhydrides in humans. There are no studies of the reproductive or genotoxic effects of cyclic acid anhydrides in humans.

Mutagenicity assays (Ames tests) using *Salmonella typhimurium* were negative for various cyclic acid anhydrides. Several cyclic acid anhydrides were negative for chromosomal aberrations in assays using Chinese hamster ovary cells or rat liver cells. These data suggest that cyclic acid anhydrides are not mutagenic or genotoxic.

Reproductive and developmental toxicity studies conducted on trimellitic anhydride, phthalic anhydride, succinic anhydride, and maleic anhydride were negative. Signs of fetotoxicity or teratogenicity were not observed.

10.2 Concentrations associated with critical effects

The critical effects of cyclic acid anhydrides are considered to be sensitization and work-related symptoms. Sensitization and work-related respiratory symptoms have been reported at concentrations as low as 10–40 $\mu g/m^3$ for trimellitic anhydride (Barker et al., 1998), 10–50 $\mu g/m^3$ of mixed exposure to hexahydrophthalic anhydride and methyl hexahydrophthalic anhydride (Welinder et al., 1994), and 5–20 $\mu g/m^3$ of exposure to methyl tetrahydrophthalic anhydride (Nielsen et al., 1992; Yokota et al., 1999).

For phthalic anhydride, the exposure level for sensitization and work-related respiratory symptoms was higher: 1500–17 400 $\mu g/m^3$ (Nielsen et al., 1988).

For tetrachlorophthalic anhydride, the exposure level for sensitization and work-related respiratory symptoms was reported to be 140–590 $\mu g/m^3$ (Liss et al., 1993), but lower concentrations, between 4.1 and 66.7 $\mu g/m^3$, have induced asthma reactions in challenge tests of sensitized workers with occupational asthma (Venables & Newman Taylor, 1990).

The critical effects in humans with the corresponding exposure levels of cyclic anhydrides for five anhydrides or groups of anhydrides are described in Table 5. Since the concentrations that trigger acute symptoms are generally lower than those concentrations that can cause sensitization, a tolerable concentration as per Environmental Health Criteria 170 (IPCS, 1994) cannot be set. Nevertheless, the exposure levels in Table 5 can be used as a helpful guideline for evaluating the risks of workplace exposure.

Table 5: Critical effects in humans with corresponding exposure levels of cyclic acid anhydrides.

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)

10.3 Uncertainties in the evaluation of health risks

The contribution of smoking and atopy as risk factors for sensitization of the anhydrides is not fully understood.

Dose–response studies of several sensitizing cyclic acid anhydrides are few or lacking.

The prognosis of asthma due to cyclic acid anhydrides is unknown.

Little is known about the exposure from products made from cyclic acid anhydrides that are used in industrial processes (e.g. exposure from thermal degradation).

When filters are not used in the sampling, exposure in particulate form may be missed. The highest exposure levels have been found where particles have been present.

Data on the carcinogenicity of anhydrides are limited. There are no studies on reproductive or genotoxic effects of cyclic acid anhydrides in humans.

11. PREVIOUS EVALUATIONS BY INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS (IOMC) BODIES

A Screening Information Data Set (SIDS) Initial Assessment Report on trimellitic anhydride and trimellitic acid was prepared for the 15th SIDS Initial Assessment Meeting, held in Boston, USA, on 22–25 October 2002 (OECD, 2002).

Succinic anhydride was evaluated by the International Agency for Research on Cancer (IARC) in 1977 (IARC, 1977). IARC classified succinic anhydride in Group 3: the agent is not classifiable as to its carcinogenicity in humans. In the only available study, succinic anhydride produced local sarcomas after subcutaneous injection in rats.

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APPENDIX 1—ACRONYMS AND ABBREVIATIONS

CAS	Chemical Abstracts Service
CI	confidence interval
CICAD	Concise International Chemical Assessment Document
ECD	electron capture detection
FID	flame ionization detection
GC	gas chromatography
GD	gestation day
HPLC	high-performance liquid chromatography
IARC	International Agency for Research on Cancer
Ig	immunoglobulin
IOMC	Inter-Organization Programme for the Sound Management of Chemicals
IPCS	International Programme on Chemical Safety
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOD	limit of detection
MITI	Ministry of International Trade and Industry (Japan)
MS	mass spectrometry
NIOSH	National Institute for Occupational Safety and Health (USA)
NOEL	no-observed-effect level
OSHA	Occupational Safety and Health Administration (USA)
PVC	polyvinyl chloride
S9	rat liver 9000 × *g* supernatant
SIDS	Screening Information Data Set
USA	United States of America
USEPA	United States Environmental Protection Agency
UV	ultraviolet
w/v	weight by volume

APPENDIX 2—SOURCE DOCUMENT

Keskinen H (2004) *The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals and the Dutch Expert Committee on Occupational Standards. 136. Cyclic acid anhydrides.* Stockholm, National Institute for Working Life, pp. 1–74 (Arbete och Hälsa NR 2004:15; http://www.inchem.org/documents/kemi/kemi/ah2004_15.pdf).

The CICAD on cyclic acid anhydrides: human health aspects was produced primarily from this report, produced under an agreement signed by the Dutch Expert Committee on Occupational Standards (DECOS) of the Health Council of the Netherlands and the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG). The purpose of the agreement is to write joint scientific criteria documents that could be used by the national regulatory authorities in both the Netherlands and the Nordic countries.

The document on health effects of cyclic acid anhydrides was written by Dr Helena Keskinen at the Finnish Institute of Occupational Health, Helsinki, Finland, and was reviewed by DECOS as well as by NEG. Editorial work and technical editing were performed by Anna-Karin Alexandrie and Jill Järnberg, NEG's scientific secretaries at the National Institute for Working Life in Sweden.

The Nordic Council was acknowledged by G.J. Mulder and G. Johanson, Chairmen of DECOS and NEG, respectively, for its financial support of the project.

APPENDIX 3—CICAD PEER REVIEW

The draft CICAD on cyclic acid anhydrides: human health aspects was sent for review to institutions and organizations identified by IPCS after contact with IPCS national Contact Points and Participating Institutions, as well as to identified experts. An open invitation to participate in the peer review process was also published on the IPCS web site. Comments were received from:

R. Benson, United States Environmental Protection Agency, Denver, CO, USA

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F. Sullivan, United Kingdom

K. Ziegler-Skylakakis, Secretariat of the Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission), Munich, Germany

APPENDIX 4—CICAD FINAL REVIEW BOARD

Helsinki, Finland
26–29 March 2007

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PHTHALIC ANHYDRIDE

ICSC: 0315
June 2003

CAS #	85-44-9	1,2-Benzenedicarboxylic acid anhydride
RTECS #	TI3150000	Phthalic acid anhydride
EC Annex 1 Index #	607-009-00-4	1,3-Isobenzofurandione
EC/EINECS #	201-607-5	$C_8H_4O_3$ / $C_6H_4(CO)_2O$
		Molecular mass: 148.1

TYPES OF HAZARD / EXPOSURE	ACUTE HAZARDS / SYMPTOMS	PREVENTION	FIRST AID / FIRE FIGHTING
FIRE	Combustible.	NO open flames.	Water spray, foam, dry powder, carbon dioxide.
EXPLOSION	Finely dispersed particles form explosive mixtures in air.	Prevent deposition of dust; closed system, dust explosion-proof electrical equipment and lighting.	
EXPOSURE		PREVENT DISPERSION OF DUST! AVOID ALL CONTACT!	
Inhalation	Cough. Sore throat. Wheezing.	Local exhaust or breathing protection.	Fresh air, rest. Half-upright position. Refer for medical attention.
Skin	Redness. Pain.	Protective gloves. Protective clothing.	Remove contaminated clothes. Rinse and then wash skin with water and soap. Refer for medical attention.
Eyes	Redness. Pain.	Safety goggles or eye protection in combination with breathing protection.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion	Abdominal pain.	Do not eat, drink, or smoke during work.	Rinse mouth. Do NOT induce vomiting. Give one or two glasses of water to drink. Refer for medical attention.

SPILLAGE DISPOSAL	PACKAGING & LABELLING
Sweep spilled substance into covered containers; if appropriate, moisten first to prevent dusting. Carefully collect remainder, then remove to safe place. Personal protection: chemical protection suit including self-contained breathing apparatus.	Do not transport with food and feedstuffs. EU Classification Symbol: Xn R: 22-37/38-41-42/43 S: (2-)23-24/25-26-37/39-46
EMERGENCY RESPONSE	STORAGE
NFPA Code: H 3; F 1; R 0	Separated from combustible and reducing substances, strong oxidants, strong bases, strong acids, food and feedstuffs. See Chemical Dangers. Ventilation along the floor. Dry. Well closed.

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SEE IMPORTANT INFORMATION ON BACK

PHTHALIC ANHYDRIDE

ICSC: 0315

IMPORTANT DATA

PHYSICAL STATE; APPEARANCE
WHITE LUSTROUS CRYSTALS , WITH CHARACTERISTIC ODOUR.

PHYSICAL DANGERS
Dust explosion possible if in powder or granular form, mixed with air.

CHEMICAL DANGERS
The substance decomposes on contact with hot water producing phthalic acid. Reacts with strong oxidants, strong acids, strong bases and reducing agents. Reacts violently on heating with copper oxide or sodium nitrite, causing explosion hazard. Attacks many metals in the presence of water.

OCCUPATIONAL EXPOSURE LIMITS
TLV: 1 ppm (as TWA) ; SEN; A4 (not classifiable as a human carcinogen); (ACGIH 2008).
MAK: IIb (not established but data is available); sensitization of respiratory tract (Sa); (DFG 2008).

ROUTES OF EXPOSURE
The substance can be absorbed into the body by inhalation of its aerosol and by ingestion.

INHALATION RISK
A harmful concentration of airborne particles can be reached quickly when dispersed, especially if powdered.

EFFECTS OF SHORT-TERM EXPOSURE
The substance is severely irritating to the eyes, the skin and the respiratory tract.

EFFECTS OF LONG-TERM OR REPEATED EXPOSURE
Repeated or prolonged contact may cause skin sensitization. Repeated or prolonged inhalation exposure may cause asthma (see Notes).

PHYSICAL PROPERTIES

Boiling point: 284°C(sublimes)
Melting point: 131°C
Density: 1.53 g/cm³

Solubility in water: slow reaction
Vapour pressure, Pa at 20°C: <0.3
Relative vapour density (air = 1): 5.1

Flash point: 152°C c.c.
Auto-ignition temperature: 570°C
Explosive limits, vol% in air: 1.7-10.4
Octanol/water partition coefficient as log Pow: 1.6

ENVIRONMENTAL DATA

NOTES

The substance may be transported in molten state. The symptoms of asthma often do not become manifest until a few hours have passed and they are aggravated by physical effort. Rest and medical observation are therefore essential. Anyone who has shown symptoms of asthma due to this substance should avoid all further contact with this substance. For materials containing more than 0.05% of maleic anhydride the UN number is 2214, hazard class 8, packaging group III and the Transport Emergency Card is TEC (R)-80S2214. Do NOT take working clothes home.Card has been partially updated in November 2008: see Occupational Exposure Limits, Ingestion First Aid.

ADDITIONAL INFORMATION

TRIMELLITIC ANHYDRIDE

ICSC: 0345
October 2005

CAS #	552-30-7	1,2,4-Benzenetricarboxylic anhydride
RTECS #	DC2050000	1,3-Dihydro-1,3-dioxo-5-isobenzofurancarboxylic acid
EC Annex 1 Index #	607-097-00-4	$C_9H_4O_5$
EC/EINECS #	209-008-0	Molecular mass: 192.2

TYPES OF HAZARD / EXPOSURE	ACUTE HAZARDS / SYMPTOMS	PREVENTION	FIRST AID / FIRE FIGHTING
FIRE	Combustible.	NO open flames.	Water spray, powder.
EXPLOSION	Finely dispersed particles form explosive mixtures in air.	Prevent build-up of electrostatic charges (e.g., by grounding). Prevent deposition of dust; closed system, dust explosion-proof electrical equipment and lighting.	
EXPOSURE		PREVENT DISPERSION OF DUST! STRICT HYGIENE!	
Inhalation	Cough. Blood stained sputum. Headache. Nausea. Shortness of breath. Wheezing. Symptoms may be delayed (see Notes).	Local exhaust or breathing protection.	Fresh air, rest. Refer for medical attention.
Skin	Redness. Pain.	Protective gloves.	Remove contaminated clothes. Rinse skin with plenty of water or shower.
Eyes	Redness. Pain.	Safety goggles or eye protection in combination with breathing protection.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion	Nausea. Abdominal pain. Burning sensation. Vomiting. Diarrhoea.	Do not eat, drink, or smoke during work.	Rinse mouth. Give one or two glasses of water to drink. Refer for medical attention.

SPILLAGE DISPOSAL	PACKAGING & LABELLING
Personal protection: P3 filter respirator for toxic particles. Sweep spilled substance into containers; if appropriate, moisten first to prevent dusting. Carefully collect remainder.	EU Classification Symbol: Xn R: 37-41-42/43 S: (2-)22-26-36/37/39
EMERGENCY RESPONSE	STORAGE
	Dry. Separated from bases and strong oxidants. Ventilation along the floor.

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TRIMELLITIC ANHYDRIDE

ICSC: 0345

IMPORTANT DATA

PHYSICAL STATE; APPEARANCE
COLOURLESS CRYSTALS OR POWDER

PHYSICAL DANGERS
Dust explosion possible if in powder or granular form, mixed with air. If dry, it can be charged electrostatically by swirling, pneumatic transport, pouring, etc.

CHEMICAL DANGERS
Reacts violently with bases and oxidants. Reacts slowly with water to form trimellitic acid.

OCCUPATIONAL EXPOSURE LIMITS
TLV: (inhalable fraction & vapour) 0.0005 mg/m³as TWA; 0.002 mg/m³ as STEL (ACGIH 2008).
MAK: (fume) 0.04 mg/m³; sensitization of respiratory tract (Sa); Peak limitation category: I(1); (DFG 2008).

ROUTES OF EXPOSURE
The substance can be absorbed into the body by inhalation and by ingestion.

INHALATION RISK
A harmful concentration of airborne particles can be reached quickly when dispersed.

EFFECTS OF SHORT-TERM EXPOSURE
The substance is irritating to the skin, the respiratory tract and is severely irritating to the eyes. Inhalation of dust may cause asthma-like reactions.

EFFECTS OF LONG-TERM OR REPEATED EXPOSURE
Repeated or prolonged inhalation exposure may cause asthma. The substance may cause allergic reactions with flu-like symptoms and 'pulmonary disease-anaemia syndrome'.

PHYSICAL PROPERTIES

Boiling point at 1.87kPa: 240-245°C
Melting point: 161-163.5°C
Solubility in water: reaction
Vapour pressure, kPa at 25°C: negligible
Relative vapour density (air = 1): 6.6

Flash point: 227°C o.c.

ENVIRONMENTAL DATA

NOTES

The symptoms of allergic reactions including asthma do not become manifest until 4 to 12 hours. Anyone who has shown symptoms of asthma due to this substance should avoid all further contact. The occupational exposure limit value should not be exceeded during any part of the working exposure. Do NOT take working clothes home. Card has been partially updated in November 2008: see Occupational Exposure Limits, Ingestion First Aid.

ADDITIONAL INFORMATION

MALEIC ANHYDRIDE

ICSC: 0799
October 2005

CAS #	108-31-6	2,5-Furandione
RTECS #	ON3675000	Dihydro-2,5-dioxofuran
UN #	2215	Maleic acid anhydride
EC Annex 1 Index #	607-096-00-9	cis-Butenedioic anhydride
EC/EINECS #	203-571-6	$C_4H_2O_3$
		Molecular mass: 98.1

TYPES OF HAZARD / EXPOSURE	ACUTE HAZARDS / SYMPTOMS	PREVENTION	FIRST AID / FIRE FIGHTING
FIRE	Combustible.	NO open flames.	Water spray. Alcohol-resistant foam. Carbon dioxide. NO powder.
EXPLOSION	Finely dispersed particles form explosive mixtures in air.	Prevent deposition of dust; closed system, dust explosion-proof electrical equipment and lighting.	
EXPOSURE		STRICT HYGIENE! PREVENT DISPERSION OF DUST!	
Inhalation	Burning sensation. Cough. Sore throat. Shortness of breath. Wheezing.	Local exhaust or breathing protection.	Fresh air, rest. Half-upright position. Refer for medical attention.
Skin	Dry skin. Redness. Pain. (See Notes).	Protective gloves. OR Heat-insulating gloves. See Notes. Protective clothing.	First rinse with plenty of water, then remove contaminated clothes and rinse again.
Eyes	Redness. Pain. Burns.	Safety goggles or eye protection in combination with breathing protection if powder.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion	Nausea. Abdominal pain. Burning sensation. Vomiting. Diarrhoea.	Do not eat, drink, or smoke during work.	Rinse mouth. Do NOT induce vomiting. Give one or two glasses of water to drink. Refer for medical attention.

SPILLAGE DISPOSAL	PACKAGING & LABELLING
Personal protection: P3 filter respirator for toxic particles. Chemical protection suit. Use face shield. Thermal gloves. See Notes. Sweep spilled substance into covered containers.	Airtight. Do not transport with food and feedstuffs. EU Classification Symbol: C R: 22-34-42/43 S: (2-)22-26-36/37/39-45 UN Classification UN Hazard Class: 8 UN Pack Group: III
EMERGENCY RESPONSE	**STORAGE**
Transport Emergency Card: TEC (R)-80S2215-S NFPA Code: H3; F1; R1;	Dry. Separated from strong oxidants, strong bases, food and feedstuffs.

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MALEIC ANHYDRIDE

ICSC: 0799

IMPORTANT DATA

PHYSICAL STATE; APPEARANCE
COLOURLESS OR WHITE CRYSTALS , WITH PUNGENT ODOUR.

CHEMICAL DANGERS
The solution in water is a medium strong acid. Reacts with strong bases and strong oxidants.

OCCUPATIONAL EXPOSURE LIMITS
TLV: 0.1 ppm as TWA; A4 (not classifiable as a human carcinogen); SEN; (ACGIH 2008).
MAK: 0.1 ppm, 0.41 mg/m³; sensitization of respiratory tract and skin (Sah); Peak limitation category: I(1); Pregnancy risk group: C; (DFG 2008).

ROUTES OF EXPOSURE
The substance can be absorbed into the body by inhalation of its aerosol, through the skin and by ingestion.

INHALATION RISK
A harmful contamination of the air can be reached rather quickly on evaporation of this substance at 20°C.

EFFECTS OF SHORT-TERM EXPOSURE
The substance is severely irritating to the eyes, the skin and the respiratory tract. Inhalation of the substance may cause asthma-like reactions.

EFFECTS OF LONG-TERM OR REPEATED EXPOSURE
Repeated or prolonged contact may cause skin sensitization. Repeated or prolonged inhalation exposure may cause asthma.

PHYSICAL PROPERTIES

Boiling point: 202°C
Melting point: 53°C
Density: 1.5 g/cm³

Solubility in water: reaction
Vapour pressure, Pa at 25°C: 25
Relative vapour density (air = 1): 3.4

Flash point: 102°C c.c.
Auto-ignition temperature: 477°C
Explosive limits, vol% in air: 1.4-7.1

ENVIRONMENTAL DATA

NOTES

Reacts violently with fire extinguishing agents such as powder. Depending on the degree of exposure, periodic medical examination is suggested. The symptoms of asthma often do not become manifest until a few hours have passed and they are aggravated by physical effort. Rest and medical observation are therefore essential. Anyone who has shown symptoms of asthma due to this substance should avoid all further contact with this substance. Maleic anhydride is transported also as hot liquid (70°C); contact of the skin should be avoided. The odour warning when the exposure limit value is exceeded is insufficient. Card has been partially updated in November 2008: see Ingestion First Aid.

ADDITIONAL INFORMATION

SUCCINIC ANHYDRIDE

ICSC: 1312
April 2006

CAS #	108-30-5	Dihydro-2,5-furandione
RTECS #	WN0875000	Butanedioic anhydride
EC Annex 1 Index #	607-103-00-5	Tetrahydro-2,5-dioxofuran
EC/EINECS #	203-570-0	$C_4H_4O_3$
		Molecular mass: 100.1

TYPES OF HAZARD / EXPOSURE	ACUTE HAZARDS / SYMPTOMS	PREVENTION	FIRST AID / FIRE FIGHTING
FIRE	Combustible. Gives off irritating or toxic fumes (or gases) in a fire.	NO open flames.	Powder, alcohol-resistant foam, water spray, carbon dioxide.
EXPLOSION	Finely dispersed particles form explosive mixtures in air.		
EXPOSURE		PREVENT DISPERSION OF DUST!	
Inhalation	Cough. Shortness of breath. Sore throat.	Local exhaust or breathing protection.	Fresh air, rest.
Skin		Protective gloves.	Rinse and then wash skin with water and soap.
Eyes	Redness. Pain.	Safety goggles, or eye protection in combination with breathing protection if powder.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion	Diarrhoea. Nausea. Vomiting.	Do not eat, drink, or smoke during work.	Rinse mouth. Give one or two glasses of water to drink.

SPILLAGE DISPOSAL	PACKAGING & LABELLING
Personal protection: P1 filter respirator for inert particles. Sweep spilled substance into covered containers; if appropriate, moisten first to prevent dusting.	EU Classification Symbol: Xi R: 36/37 S: (2-)25 GHS Classification Warning Harmful if swallowed Causes serious eye irritation
EMERGENCY RESPONSE	STORAGE
NFPA Code: H1; F1; R; 0	

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SUCCINIC ANHYDRIDE

ICSC: 1312

IMPORTANT DATA

PHYSICAL STATE; APPEARANCE
COLOURLESS CRYSTALS OR FLAKES

CHEMICAL DANGERS
The substance decomposes on heating producing irritating fumes.

OCCUPATIONAL EXPOSURE LIMITS
TLV not established. MAK not established.

ROUTES OF EXPOSURE
The substance can be absorbed into the body by inhalation and by ingestion.

INHALATION RISK
A harmful concentration of airborne particles can be reached quickly when dispersed, especially if powdered.

EFFECTS OF SHORT-TERM EXPOSURE
The substance is severely irritating to the eyes and is irritating to the respiratory tract.

PHYSICAL PROPERTIES

Boiling point: 261°C
Melting point: 119.6°C
Relative density (water = 1): 1.503
Solubility in water: none
Vapour pressure, kPa at 92°C: 1.3
Relative vapour density (air = 1): 3.45

Flash point: 157°C

ENVIRONMENTAL DATA

NOTES

ADDITIONAL INFORMATION

TETRAHYDROPHTHALIC ANHYDRIDE

ICSC: 1372
March 2001

CAS #	85-43-8	4-Cyclohexene-1,2-dicarboxylic anhydride
RTECS #	GW5775000	3a,4,7,7a-Tetrahydro-1,3-isobenzofurandione
UN #	2698	THPA
EC Annex 1 Index #	607-099-00-5	1,2,3,6-Tetrahydrophthalic anhydride
EC/EINECS #	201-605-4	$C_8H_8O_3$ / $C_6H_8(CO)_2O$
		Molecular mass: 152.2

TYPES OF HAZARD / EXPOSURE	ACUTE HAZARDS / SYMPTOMS	PREVENTION	FIRST AID / FIRE FIGHTING
FIRE	Combustible.	NO open flames.	Powder, water spray, foam, carbon dioxide.
EXPLOSION			
EXPOSURE		PREVENT DISPERSION OF DUST!	
Inhalation	Cough. Sore throat. Wheezing. Shortness of breath.	Local exhaust or breathing protection.	Fresh air, rest. Half-upright position. Refer for medical attention.
Skin	Redness. Burning sensation.	Protective gloves. Protective clothing.	Remove contaminated clothes. Rinse skin with plenty of water or shower.
Eyes	Redness. Pain. Blurred vision. Severe deep burns.	Safety goggles, or eye protection in combination with breathing protection.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion	Burning sensation.	Do not eat, drink, or smoke during work. Wash hands before eating.	Rinse mouth. Do NOT induce vomiting.

SPILLAGE DISPOSAL

Sweep spilled substance into containers; if appropriate, moisten first to prevent dusting. Carefully collect remainder, then remove to safe place. Do NOT let this chemical enter the environment. (Extra personal protection: P2 filter respirator for harmful particles.)

PACKAGING & LABELLING

Do not transport with food and feedstuffs.
EU Classification
Symbol: Xn
R: 41-42/43-52/53
S: (2-)22-24-26-37/39-61
Note: C
UN Classification
UN Hazard Class: 8
UN Pack Group: III

EMERGENCY RESPONSE

Transport Emergency Card: TEC (R)-80G09c

STORAGE

Separated from food and feedstuffs. Dry. Well closed.

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TETRAHYDROPHTHALIC ANHYDRIDE

ICSC: 1372

IMPORTANT DATA

PHYSICAL STATE; APPEARANCE
WHITE CRYSTALLINE POWDER

CHEMICAL DANGERS
The substance decomposes on contact with hot surfaces or flames producing corrosive fumes. Reacts with oxidants. Reacts with water to produce heat and tetrahydrophthalic acid.

OCCUPATIONAL EXPOSURE LIMITS
TLV not established. MAK not established.

ROUTES OF EXPOSURE
The substance can be absorbed into the body by inhalation of its aerosol.

INHALATION RISK
Evaporation at 20°C is negligible; a harmful concentration of airborne particles can, however, be reached quickly when dispersed.

EFFECTS OF SHORT-TERM EXPOSURE
The substance is irritating to the eyes, the skin and the respiratory tract.

EFFECTS OF LONG-TERM OR REPEATED EXPOSURE
Repeated or prolonged contact may cause skin sensitization. Repeated or prolonged inhalation exposure may cause asthma.

PHYSICAL PROPERTIES

Boiling point at 6.7 kPa:	195°C	Flash point:	157°C o.c.
Melting point:	102°C	Auto-ignition temperature:	450°C
Density:	1.4 g/cm³		
Solubility in water:	reaction		
Vapour pressure, Pa at 20°C:	1		
Relative vapour density (air = 1):	5.3		

ENVIRONMENTAL DATA

The substance is harmful to aquatic organisms.

NOTES

The symptoms of asthma often do not become manifest until a few hours have passed and they are aggravated by physical effort. Rest and medical observation are therefore essential. Anyone who has shown symptoms of asthma due to this substance should avoid all further contact with this substance. For cis-isomer the CAS number is 935-79-5.

ADDITIONAL INFORMATION

CHLORENDIC ANHYDRIDE

ICSC: 1373
March 2001

CAS #	115-27-5	4,5,6,7,8,8-Hexachloro-3a,4,7,7a-tetrahydro-4,7-methanoisobenzofuran-1,3-dione
RTECS #	RB9080000	
EC Annex 1 Index #	607-101-00-4	1,4,5,6,7,7-Hexachloro-endo-5-norbornene-2,3-dicarboxylic anhydride
EC/EINECS #	204-077-3	Hexachloro-endo-methylene tetrahydrophthalic anhydride
		$C_9H_2Cl_6O_3$
		Molecular mass: 370.8

TYPES OF HAZARD / EXPOSURE	ACUTE HAZARDS / SYMPTOMS	PREVENTION	FIRST AID / FIRE FIGHTING
FIRE	Not combustible. Gives off irritating or toxic fumes (or gases) in a fire.		In case of fire in the surroundings: use appropriate extinguishing media.
EXPLOSION			
EXPOSURE		PREVENT DISPERSION OF DUST!	
Inhalation	Cough. Sore throat. Wheezing. Shortness of breath.	Local exhaust or breathing protection.	Fresh air, rest. Half-upright position. Refer for medical attention.
Skin	Redness. Burning sensation.	Protective gloves. Protective clothing.	Remove contaminated clothes. Rinse skin with plenty of water or shower.
Eyes	Redness. Pain.	Safety goggles, or eye protection in combination with breathing protection.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion	Burning sensation.	Do not eat, drink, or smoke during work. Wash hands before eating.	Rinse mouth. Do NOT induce vomiting.

SPILLAGE DISPOSAL	PACKAGING & LABELLING
Sweep spilled substance into containers; if appropriate, moisten first to prevent dusting. Wash away remainder with plenty of water. (Extra personal protection: P2 filter respirator for harmful particles.)	EU Classification Symbol: Xi R: 36/37/38 S: (2-)25
EMERGENCY RESPONSE	STORAGE
	Dry. Well closed.

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CHLORENDIC ANHYDRIDE

ICSC: 1373

IMPORTANT DATA

PHYSICAL STATE; APPEARANCE
WHITE CRYSTALS

CHEMICAL DANGERS
Reacts with water to produce chlorendic acid.

OCCUPATIONAL EXPOSURE LIMITS
TLV not established. MAK not established.

ROUTES OF EXPOSURE
The substance can be absorbed into the body by inhalation of its aerosol.

INHALATION RISK
Evaporation at 20°C is negligible; a harmful concentration of airborne particles can, however, be reached quickly when dispersed.

EFFECTS OF SHORT-TERM EXPOSURE
The substance is irritating to the eyes, the skin and the respiratory tract.

EFFECTS OF LONG-TERM OR REPEATED EXPOSURE
Repeated or prolonged contact may cause skin sensitization. Repeated or prolonged inhalation exposure may cause asthma.

PHYSICAL PROPERTIES

Melting point:	231-235°C
Density:	1.73 g/cm³
Solubility in water:	reaction

ENVIRONMENTAL DATA

NOTES

The symptoms of asthma often do not become manifest until a few hours have passed and they are aggravated by physical effort. Rest and medical observation are therefore essential. Anyone who has shown symptoms of asthma due to this substance should avoid all further contact with this substance.

ADDITIONAL INFORMATION

TETRACHLOROPHTHALIC ANHYDRIDE

ICSC: 1374
March 2001

CAS #	117-08-8	4,5,6,7-Tetrachloro-1,3-isobenzofurandione
RTECS #	TI3450000	1,3-Dioxy-4,5,6,7-tetrachloroisobenzofuran
EC Annex 1 Index #	607-242-00-1	$C_8Cl_4O_3$ / $C_6Cl_4(CO)_2O$
EC/EINECS #	204-171-4	Molecular mass: 285.9

TYPES OF HAZARD / EXPOSURE	ACUTE HAZARDS / SYMPTOMS	PREVENTION	FIRST AID / FIRE FIGHTING
FIRE	Combustible. Gives off irritating or toxic fumes (or gases) in a fire.	NO open flames.	Water spray, powder.
EXPLOSION			
EXPOSURE		PREVENT DISPERSION OF DUST!	
Inhalation	Cough. Sore throat. Wheezing. Shortness of breath.	Local exhaust or breathing protection.	Fresh air, rest. Half-upright position. Refer for medical attention.
Skin	Redness. Burning sensation.	Protective gloves. Protective clothing.	Remove contaminated clothes. Rinse skin with plenty of water or shower.
Eyes	Redness. Pain. Blurred vision.	Safety goggles, or eye protection in combination with breathing protection.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion	Burning sensation.	Do not eat, drink, or smoke during work. Wash hands before eating.	Rinse mouth. Do NOT induce vomiting.

SPILLAGE DISPOSAL	PACKAGING & LABELLING
Sweep spilled substance into containers; if appropriate, moisten first to prevent dusting. Carefully collect remainder, then remove to safe place. Do NOT let this chemical enter the environment. (Extra personal protection: P2 filter respirator for harmful particles.)	EU Classification Symbol: Xn, N R: 41-42/43-50/53 S: (2-)22-24-26-37/39-60-61
EMERGENCY RESPONSE	STORAGE
	Dry. Well closed.

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TETRACHLOROPHTHALIC ANHYDRIDE

ICSC: 1374

IMPORTANT DATA

PHYSICAL STATE; APPEARANCE
WHITE POWDER

CHEMICAL DANGERS
Reacts slowly with water to produce acid.

OCCUPATIONAL EXPOSURE LIMITS
TLV not established. MAK not established.

ROUTES OF EXPOSURE
The substance can be absorbed into the body by inhalation of its aerosol.

INHALATION RISK
Evaporation at 20°C is negligible; a harmful concentration of airborne particles can, however, be reached quickly when dispersed.

EFFECTS OF SHORT-TERM EXPOSURE
The substance is irritating to the eyes, the skin and the respiratory tract.

EFFECTS OF LONG-TERM OR REPEATED EXPOSURE
Repeated or prolonged contact may cause skin sensitization. Repeated or prolonged inhalation exposure may cause asthma.

PHYSICAL PROPERTIES

Boiling point: 371°C
Melting point: 255°C
Solubility in water, g/100 ml at 20°C: 0.4

Flash point: 362°C c.c.

ENVIRONMENTAL DATA

NOTES

The symptoms of asthma often do not become manifest until a few hours have passed and they are aggravated by physical effort. Rest and medical observation are therefore essential. Anyone who has shown symptoms of asthma due to this substance should avoid all further contact with this substance.

ADDITIONAL INFORMATION

PYROMELLITIC DIANHYDRIDE

ICSC: 1375
March 2001

CAS #	89-32-7	1,2,4,5-Benzenetetracarboxylic 1,2:4,5-dianhydride
RTECS #	DB9300000	1,2,4,5-Benzenetetracarboxylic anhydride
EC Annex 1 Index #	607-098-00-X	1H,3H-Benzo(1,2-c;4,5-c')difuran-1,3,5,7-tetrone
EC/EINECS #	201-898-9	PMDA
		$C_{10}H_2O_6$ / $C_6H_2(C_2O_3)_2$
		Molecular mass: 218.1

TYPES OF HAZARD / EXPOSURE	ACUTE HAZARDS / SYMPTOMS	PREVENTION	FIRST AID / FIRE FIGHTING
FIRE	Combustible.	NO open flames.	Powder, water spray, foam, carbon dioxide.
EXPLOSION			
EXPOSURE		PREVENT DISPERSION OF DUST!	
Inhalation	Cough. Sore throat. Wheezing. Shortness of breath.	Local exhaust or breathing protection.	Fresh air, rest. Half-upright position. Refer for medical attention.
Skin	Redness. Burning sensation.	Protective gloves. Protective clothing.	Remove contaminated clothes. Rinse skin with plenty of water or shower.
Eyes	Redness. Pain. Blurred vision.	Safety goggles, or eye protection in combination with breathing protection.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion	Burning sensation.	Do not eat, drink, or smoke during work. Wash hands before eating.	Rinse mouth. Do NOT induce vomiting.

SPILLAGE DISPOSAL	PACKAGING & LABELLING
Sweep spilled substance into containers; if appropriate, moisten first to prevent dusting. Wash away remainder with plenty of water. (Extra personal protection: P2 filter respirator for harmful particles.)	EU Classification Symbol: Xn R: 41-42/43 S: (2-)22-24-26-37/39
EMERGENCY RESPONSE	STORAGE
	Dry. Well closed.

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PYROMELLITIC DIANHYDRIDE

ICSC: 1375

IMPORTANT DATA

PHYSICAL STATE; APPEARANCE
WHITE HYGROSCOPIC CRYSTALLINE POWDER , WITH CHARACTERISTIC ODOUR.

CHEMICAL DANGERS
Reacts with water to produce acid.

OCCUPATIONAL EXPOSURE LIMITS
TLV not established. MAK not established.

ROUTES OF EXPOSURE
The substance can be absorbed into the body by inhalation of its aerosol.

INHALATION RISK
Evaporation at 20°C is negligible; a harmful concentration of airborne particles can, however, be reached quickly when dispersed.

EFFECTS OF SHORT-TERM EXPOSURE
The substance is irritating to the eyes, the skin and the respiratory tract. Exposure at high levels may result in pulmonary hemorrhage.

EFFECTS OF LONG-TERM OR REPEATED EXPOSURE
Repeated or prolonged contact may cause skin sensitization. Repeated or prolonged inhalation exposure may cause asthma.

PHYSICAL PROPERTIES

Boiling point:	397-400°C
Melting point:	287°C
Density:	1.68 g/cm³
Solubility in water:	reaction

ENVIRONMENTAL DATA

NOTES

The symptoms of asthma often do not become manifest until a few hours have passed and they are aggravated by physical effort. Rest and medical observation are therefore essential. Anyone who has shown symptoms of asthma due to this substance should avoid all further contact with this substance.

ADDITIONAL INFORMATION

CYCLOHEXANEDICARBOXYLIC ACID ANHYDRIDE

ICSC: 1643
November 2006

CAS # 85-42-7
EC Annex 1 Index # 607-102-00-X
EC/EINECS # 201-604-9

1,3-Isobenzofurandione, hexahydro-
Cyclohexane-1,2-dicarboxylic acid anhydride
Hexahydro-isobenzofuran-1,3-dione
Hexahydrophthalic anhydride
HHPA
$C_8H_{10}O_3$
Molecular mass: 154.2

TYPES OF HAZARD / EXPOSURE	ACUTE HAZARDS / SYMPTOMS	PREVENTION	FIRST AID / FIRE FIGHTING
FIRE	Combustible. Gives off irritating or toxic fumes (or gases) in a fire.	NO open flames.	water in large amounts,
EXPLOSION			
EXPOSURE		AVOID ALL CONTACT!	
Inhalation	Cough. Wheezing. Symptoms may be delayed (see Notes).	Ventilation, local exhaust, or breathing protection.	Fresh air, rest. Refer for medical attention.
Skin	Redness.	Protective gloves. Protective clothing.	Remove contaminated clothes. Rinse and then wash skin with water and soap.
Eyes	Redness. Pain.	Face shield and eye protection in combination with breathing protection.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion	Sore throat. Burning sensation. Abdominal pain. Diarrhoea.	Do not eat, drink, or smoke during work.	Rinse mouth. Refer for medical attention.

SPILLAGE DISPOSAL

Personal protection: complete protective clothing including self-contained breathing apparatus. Sweep spilled substance into covered containers. Do NOT let this chemical enter the environment.

PACKAGING & LABELLING

EU Classification
Symbol: Xn
R: 41-42/43
S: (2-)23-24-26-37/39
Note: C
GHS Classification
Danger
May cause allergic or asthmatic symptoms or breathing difficulties if inhaled
May cause allergic skin reaction
Causes serious eye irritation
Causes skin irritation
Harmful to aquatic life

EMERGENCY RESPONSE

STORAGE

Dry. Store in an area without drain or sewer access.

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CYCLOHEXANEDICARBOXYLIC ACID ANHYDRIDE ICSC: 1643

IMPORTANT DATA

PHYSICAL STATE; APPEARANCE
SOLID IN VARIOUS FORMS.

CHEMICAL DANGERS
The substance decomposes slowly on contact with water producing acids.

OCCUPATIONAL EXPOSURE LIMITS
TLV: (Inhalable fraction & vapour) 0.005 mg/m³ (Ceiling value); SEN (ACGIH 2008).
MAK: sensitization of respiratory tract (Sa); (DFG 2008).

ROUTES OF EXPOSURE
The substance can be absorbed into the body by inhalation.

INHALATION RISK
A harmful concentration of airborne particles can be reached quickly when dispersed, especially if powdered.

EFFECTS OF SHORT-TERM EXPOSURE
The substance is irritating to the skin and is severely irritating to the eyes

EFFECTS OF LONG-TERM OR REPEATED EXPOSURE
Repeated or prolonged contact may cause skin sensitization. Repeated or prolonged inhalation exposure may cause asthma.

PHYSICAL PROPERTIES

Boiling point: 296°C
Melting point: 35-36°C
Solubility in water: reaction
Vapour pressure, Pa at 25°C: 0.9
Relative vapour density (air = 1): 5.3

Octanol/water partition coefficient as log Pow: 21.4

ENVIRONMENTAL DATA

The substance is harmful to aquatic organisms.

NOTES

The symptoms of asthma often do not become manifest until a few hours have passed and they are aggravated by physical effort. Rest and medical observation are therefore essential. Card has been partially updated in November 2008: see Occupational Exposure Limits, GHS classification.

ADDITIONAL INFORMATION

METHYLTETRAHYDROPHTHALIC ANHYDRIDE

ICSC: 1645
April 2008

CAS #	26590-20-5	Tetrahydromethyl-1,3-isobenzofuranedione
RTECS #	I3325000	MTHPA
EC Annex 1 Index #	607-240-00-0	1,2,3,6-tetrahydromethylphthalic anhydride
EC/EINECS #	247-830-1	1,3-Isobenzofurandione, 3a,4,7,7a-tetrahydromethyl-
		$C_9H_{10}O_3$
		Molecular mass: 166.2

TYPES OF HAZARD / EXPOSURE	ACUTE HAZARDS / SYMPTOMS	PREVENTION	FIRST AID / FIRE FIGHTING
FIRE	Combustible.	NO open flames.	In case of fire in the surroundings: use appropriate extinguishing media.
EXPLOSION			
EXPOSURE		AVOID ALL CONTACT!	
Inhalation	Cough.	Ventilation, local exhaust, or breathing protection.	Fresh air, rest.
Skin	Redness.	Protective gloves. Protective clothing.	Remove contaminated clothes. Rinse and then wash skin with water and soap. Refer for medical attention if skin irritation occurs
Eyes	Redness.	Face shield and eye protection in combination with breathing protection.	Rinse with plenty of water (remove contact lenses if easily possible).
Ingestion		Do not eat, drink, or smoke during work.	Rinse mouth.

SPILLAGE DISPOSAL	PACKAGING & LABELLING
Chemical protection suit including self-contained breathing apparatus. Collect leaking liquid in covered containers.	EU Classification Symbol: Xn R: 41-42/43 S: (2-)22-24-26-37/39 Note: C GHS Classification Danger May cause allergic or asthmatic symptoms or breathing difficulties if inhaled May cause allergic skin reaction
EMERGENCY RESPONSE	STORAGE

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International Programme on Chemical Safety

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METHYLTETRAHYDROPHTHALIC ANHYDRIDE

ICSC: 1645

IMPORTANT DATA

PHYSICAL STATE; APPEARANCE
OILY LIQUID

OCCUPATIONAL EXPOSURE LIMITS
TLV not established.
MAK not established.

ROUTES OF EXPOSURE
The substance can be absorbed into the body by inhalation.

EFFECTS OF LONG-TERM OR REPEATED EXPOSURE
Repeated or prolonged inhalation exposure may cause asthma see notes. The substance may have effects on the skin, resulting in contact urticaria.

PHYSICAL PROPERTIES

Boiling point: 124°C
Melting point: -29°C

Flash point: 350°C

ENVIRONMENTAL DATA

NOTES

The symptoms of asthma often do not become manifest until a few hours have passed and they are aggravated by physical effort. Rest and medical observation are therefore essential. Anyone who has shown symptoms of asthma due to this substance should avoid all further contact.

ADDITIONAL INFORMATION

RÉSUMÉ D'ORIENTATION

Le présent CICAD[1] (Concise International Chemical Assessment Document/Document concis d'évaluation chimique internationale) relatif aux anhydrides d'acide cycliques a été préparé par Sciences International, Inc. Il s'inspire d'une étude effectuée par le Groupe nordique d'experts pour les documents de critères relatifs aux risques sanitaires des produits chimiques et par le Comité néerlandais d'experts sur les normes professionnelles (Keskinen, 2004). Afin de prendre en compte les références qui ne figurent pas dans ladite étude, il a été procédé en juin 2006 à une recherche bibliographique exhaustive portant sur plusieurs bases de données en ligne. L'appendice 2 donne des renseignements sur l'étude initiale et sur son examen par des pairs. Des informations sur l'examen par des pairs du présent CICAD figurent l'appendice 3. Ce CICAD a été examiné et approuvé en tant qu'évaluation internationale lors la réunion du Comité d'évaluation finale qui s'est tenue à Helsinki (Finlande) du 26 au 29 mars 2007. La liste des participants à cette réunion figure à l'appendice 4. Les fiches internationales sur la sécurité chimique de plusieurs anhydrides d'acide cycliques établie par le Programme international sur la sécurité chimique (IPCS/PISC) sont également reproduites dans le présent CICAD (IPCS, 2000a,b,c,d, 2005a,b,c,d,e, 2006).

L'industrie chimique fait un large usage des anhydrides d'acide cycliques. Ces composés sont irritants et ce sont des agents sensibilisants particulièrement puissants. Parmi les plus courants d'entre eux, on peut citer : l'anhydride phtalique, l'anhydride trimélitique, l'anhydride maléique, l'anhydrique hexahydrophtalique, l'anhydride méthylhexahydrophtalique, l'anhydride méthyl-tétrahydrophtalique, l'anhydride tétrahydrophtalique, l'anhydride tétrachlorophtalique, le dianhydride pyroméllitique, l'anhydride himique, l'anhydride succinique, l'anhydride dodécènylsuccinique, l'anhydride chlorendique et l'anhydride tétrabromo-phtalique.

Pour prélever des échantillons de vapeurs d'anhydrides d'acide cycliques ont utilise des tubes à absorbant solide, des barboteurs ou des impacteurs. Les barboteurs et les impacteurs échantillonnent l'anhydride sous forme de l'acide correspondant. Pour les prélèvements de particules, on utilise soit un impacteur, soit un barboteur et des filtres en chlorure de polyvinyle (PVC) ou en Téflon disposés en série avec des tubes à absorbant solide. Pour recueillir à la fois des particules et des vapeurs, il est recommandé d'utiliser les deux méthodes d'échantillonnage lorsqu'on ignore sous quelle forme il y a eu exposition. Pour l'analyse des échantillons, on peut procéder par chromatographie en phase gazeuse avec détection par ionisation de flamme, capture d'électrons ou spectrométrie de masse.

Après esterification, la recherche et le dosage dans l'urine des acides dicarboxyliques correspondant aux divers anhydrides s'effectue par chromatographie en phase gazeuse avec détection soit par capture d'électrons, soit par spectrométrie de masse. On a également mis au point une méthode pour la recherche et le dosage des anhydrides dans le plasma.

Les anhydrides d'acide cycliques sont utilisés principalement pour la production de polyesters et de résines alkydes et on les emploie également comme plastifiants ou comme durcissants dans les résines époxy. Ces composés se présentent essentiellement sous forme pulvérulente ou cristalline.

On ne dispose pas d'informations sur le transport, la distribution et la transformation des anhydrides d'acide cycliques dans l'environnement. Au vu de ses propriétés chimiques, l'anhydride phtalique devrait être rapidement hydrolysé en acide phtalique dans l'environnement aquatique et dans les sols humides. Etant donné sa faible tension de vapeur, cet anhydride ne doit pas se volatiliser en quantité importante lorsqu'il est présent dans l'eau ou le sol. Dans l'air, l'anhydride phtalique va réagir avec les radicaux hydroxyles.

Les anhydrides d'acide cycliques sont principalement absorbés par inhalation, mais on a également fait état d'une absorption par la voie transdermique. Des études portant sur l'inhalation d'anhydrides d'acide cycliques par des sujets humains montrent qu'ils sont excrétés dans l'urine sous la forme des acides dicarboxyliques correspondants. L'étude de la répartition tissulaire de ces composés chez des animaux de laboratoire révèle que c'est au niveau des muqueuses nasales et trachéennes que leur concentration est la plus élevée.

Le reste anhydride réagit sur les acides aminés pour former des conjugués protéiques, par exemple avec l'albumine du sérum. Les travailleurs exposés sur leur lieu de travail présentent des concentrations mesurables d'adduits avec les protéines plasmatiques et notamment avec l'albumine. Des études chimiques portant sur leur interaction avec les protéines ont montré que l'acide aminé auquel les anhydrides d'acide cycliques se fixent préférentiellement est la lysine.

La demi-vie des anhydrides d'acide cycliques dans l'urine humaine varie de 2 - 3 h dans le cas de l'acide hexahydrophtalique à 14 h dans le cas de l'acide

[1] La liste complète des acronymes et abréviations utilisés dans le présent rapport se trouve à l'appendice 1.

phtalique. Dans le plasma, on a observé une demi-vie de 1,7 à 1,8 h dans le cas de l'acide hexahydrophtalique.

Chez l'animal, la toxicité aiguë exprimée sous la forme de la dose létale médiane (DL_{50}) va de 75,5 mg/kg de poids corporel à plus de 15 800 mg/kg pc lorsque les composés sont administrés par la voie respiratoire, transdermique ou intrapéritonéale. Ce sont l'anhydride phtalique et l'anhydride maléique qui présentent la DL_{50} la plus faible par voie orale. L'expérimentation animale montre que l'anhydride maléique et l'anhydride triméllitique sont des irritants oculaires extrêmement puissants.

Une exposition de moyenne durée à ces composés a produit chez l'animal une irritation tissulaire nasale se traduisant par une hyperplasie et une métaplasie. On a constaté que ces réactions inflammatoires de la muqueuse nasale étaient réversibles.

Il n'existe guère d'études comportant une exposition de longue durée ou d'études de cancérogénicité de ces composés chez l'animal. Des études au cours desquelles on a administré par voie alimentaire de l'anhydride phtalique à des rongeurs pendant une longue période n'ont mis en évidence aucun signe de cancérogénicité. Lors d'une étude limitée sur des rats soumis à des injections sous-cutanées d'anhydride succinique, on a observé des sarcomes sous-cutanés au point d'injection.

La base de données sur la mutagénicité et la génotoxicité des anhydrides d'acide cycliques est limitée. Le test d'Ames sur *Salmonella typhimurium* et la recherche d'aberrations chromosomiques effectués sur plusieurs de ces composés n'ont permis de mettre en évidence ni mutagénicité, ni génotoxicité.

En ce qui concerne la reprotoxicité et les effets sur le développement, la base de données n'est guère fournie. On n'a pas constaté d'effets reprotoxiques ni d'effets nocifs sur le développement après administration d'anhydride maléique à des femelles gestantes. Lors d'une étude consacrée aux effets de l'anhydride phtalique et de l'anhydride succinique sur le développement, on a observé des malformations congénitales sur des souriceaux exposés pendant la gestation, mais uniquement à des doses également toxiques pour la mère. Cela étant, cette étude a utilisé la voie intrapéritonéale pour administrer les composés, voie dont l'importance est discutable s'agissant de l'exposition humaine.

De nombreux travaux d'expérimentation animale ont été consacrés à l'évaluation des effets sensibilisateurs afin de caractériser la nature et les paramètres de la réponse immunitaire suscitée par ces composés et pour élucider leur mode d'action. Plusieurs de ces études sont parvenues à la conclusion que les anhydrides d'acide cycliques ne provoquent pas de dermatites allergiques de contact chez les rongeurs. Les études de sensibilisation consistent généralement à sensibiliser l'animal à un anhydride d'acide cyclique puis à l'exposer à un conjugué albumine sérique- anhydride. Plus précisément, on a évalué la réponse immunitaire après l'exposition d'épreuve en mesurant le taux d'anticorps et en recherchant la présence de foyers hémorragiques pulmonaires. Une relation dose-réponse significative a été observée entre la réponse immunitaire et l'exposition à plusieurs anhydrides d'acide cycliques. Les anticorps dont on observe habituellement une augmentation du taux après sensibilisation et exposition d'épreuve sont des immunoglobulines E (IgE) ainsi que des IgG, qui réagissent vis-à-vis du conjugué albumine sérique-anhydride étudié. Chez des rats sensibilisés puis soumis à une exposition d'épreuve à de l'anhydride triméllitique, on a relevé une augmentation du nombre de foyers hémorragiques pulmonaires ainsi qu'une hyperréactivité bronchique.

Il existe une autre méthode pour étudier les effets sensibilisateurs des anhydrides d'acide cycliques qui consiste à inhiber certains éléments du système et de la réponse immunitaires pour voir s'il y a également inhibition de la sensibilisation. Des études au cours desquelles on a utilisé du venin de cobra pour inhiber l'activation du complément n'ont révélé aucun effet sur la bronchoconstriction ou la fuite microvasculaire immédiates, mais il y avait inhibition de l'infiltration cellulaire inflammatoire en présence d'un asthme provoqué par l'anhydride triméllitique. On a montré que la déplétion des macrophages alvéolaires pulmonaires induite par le clodronate atténuait la réduction de la fonction pulmonaire induite par l'exposition à l'anhydride d'acide cyclique, mais augmentait les lésions et l'inflammation tissulaires 24 h après l'exposition d'épreuve.

Selon les études consacrées au mode d'action des anhydrides d'acide cycliques chez l'Homme, ces composés provoquent un urticaire ainsi qu'un asthme allergique à médiation anticorpale (IgE). Cet asthme allergique est souvent précédé par une rhinoconjonctivite médiée par les IgE. L'expérimentation animale montre que l'histamine et le thromboxane A_2 sont responsables des réactions bronchoconstrictives précoces et retardées à l'anhydride triméllitique. On a également constaté une exsudation au niveau des voies aériennes médiée par les leucotriènes et l'histamine. L'administration de divers traitements immunosuppresseurs provoque l'inhibition de l'hyperréactivité des voies aériennes, des lésions pulmonaires et de la réponse anticorpale aux anhydrides d'acide cycliques.

Chez les sujets humains, les anhydrides d'acide cycliques peuvent provoquer une irritation et une sensibilisation après contact direct avec la peau ou les

muqueuses ou encore après exposition par inhalation. L'irritation est due à l'acide dicarboxylique qui se forme lorsque l'anhydride cyclique réagit avec l'eau. Les pathologies allergiques les plus courantes sont la rhinoconjonctivite et l'asthme, qui sont toutes deux des allergies immédiates médiées par les IgE.

En raison des propriétés sensibilisantes des anhydrides d'acide cycliques, il n'est pas possible d'établir de concentrations tolérables conformément aux recommandations du No 170 de la Série des Critères d'hygiène de l'environnement. A titre indicatif et pour permettre d'évaluer les risques d'exposition à un certain nombre de ces anhydrides sur le lieu de travail, on peut obtenir la fourchette de concentration dans laquelle les divers composés provoquent une sensibilisation ou autres effets. La concentration la plus faible de l'un quelconque de ces composés qui ait provoqué des effets est égale à 5 $\mu g/m^3$ (anhydride méthyltétrahydrophtalique). Par contre, la concentration la plus faible d'anhydride phtalique susceptible de provoquer un effet est égale à 1500 $\mu g/m^3$.

RESUMEN DE ORIENTACIÓN

El presente documento abreviado de evaluación internacional de productos químicos (CICAD)[1] sobre los anhídridos ácidos cíclicos fue preparado por Sciences International, Inc. y se basó en un examen efectuado por el Grupo nórdico de expertos para la documentación de criterios sobre los riesgos sanitarios de los productos químicos y el Comité de expertos holandés sobre normas ocupacionales (Keskinen, 2004). Para tener en cuenta la bibliografía no incluida en dicho examen, en junio de 2006 se efectuó una búsqueda bibliográfica exhaustiva en varias bases de datos en línea. En el apéndice 2 se presenta la información sobre el documento fuente y su revisión por expertos. En el apéndice 3 se presenta la información sobre la revisión por expertos de este CICAD, que fue examinado y aprobado tras una evaluación internacional en una reunión del Comité de evaluación final celebrada en Helsinki (Finlandia) del 26 al 29 de marzo de 2007. En el apéndice 4 figura la lista de participantes en la reunión del Comité de evaluación final. En el presente CICAD se reproducen las fichas internacionales de seguridad química de varios anhídridos ácidos cíclicos (IPCS, 2000a, b, c, d, 2005a, b, c, d, e, 2006) producidas por el Programa Internacional de Seguridad de las Sustancias Químicas (IPCS).

Los anhídridos ácidos cíclicos se utilizan mucho en la industria química. Los anhídridos ácidos son irritantes y sensibilizantes especialmente potentes. Entre los anhídridos ácidos cíclicos comunes se encuentran los anhídridos ftálico, trimelítico, maleico, hexahidroftálico, metilhexahidroftálico, metiltetrahidroftálico, tetrahidroftálico, tetracloroftálico, hímico, succínico, dodecenilsuccínico, cloréndico y tetrabromoftálico, y el dianhídrido piromelítico.

Para recoger muestras de vapores de anhídridos ácidos cíclicos se utilizan tubos con adsorbentes sólidos, borboteadores e impactadores. Usando borboteadores e impactadores se obtiene a partir del anhídrido el ácido correspondiente. Para la obtención de muestras de partículas se utilizan los métodos del impactador o el borboteador y filtros de cloruro de polivinilo (PVC) o Teflón en serie con tubos de adsorbentes sólidos. Para recuperar tanto partículas como vapores, se recomienda el muestreo con ambos métodos en los estudios en los que se desconozca el estado de exposición. Para analizar las muestras se ha utilizado la cromatografía de gases con detección mediante ionización de llama, captura de electrones o espectrometría de masas.

Los ácidos dicarboxílicos de varios anhídridos presentes en la orina han sido analizados, tras la

[1] Véase en el apéndice 1 la lista completa de las abreviaciones y acrónimos utilizados en este informe.

esterificación, por cromatografía de gases con detección mediante captura de electrones o espectrometría de masas. También se ha desarrollado un método para analizar anhídridos presentes en el plasma.

Los anhídridos ácidos cíclicos se utilizan sobre todo en la fabricación de poliéster, resinas alquido y plastificantes, y también como endurecedores de resinas epoxi. Los anhídridos ácidos cíclicos son principalmente polvos o cristales.

No hay información sobre el transporte, distribución y transformación de anhídridos ácidos cíclicos en el medio ambiente. Dadas sus propiedades químicas, se supone que en medios acuosos y en el suelo húmedo el anhídrido ftálico sufre una hidrólisis rápida, convirtiéndose en ácido ftálico. Dada su baja presión de vapor, el anhídrido ftálico no sufrirá una volatilización importante a partir del agua o del suelo; en el aire, reaccionará con radicales hidroxilo.

Los anhídridos ácidos cíclicos se absorben principalmente por inhalación, aunque también se ha descrito su absorción transdérmica. Los estudios sobre la inhalación de anhídridos ácidos cíclicos en el ser humano han demostrado la excreción urinaria del ácido dicarboxílico correspondiente. Los estudios en animales en los que se ha evaluado la distribución tisular de los anhídridos ácidos cíclicos han revelado que las mayores concentraciones se encuentran en la mucosa nasal y traqueal.

La fracción anhídrido reacciona fácilmente con los aminoácidos, formando conjugados con las proteínas, como la seroalbúmina. Los trabajadores sometidos a exposición laboral presentan concentraciones detectables de aductos con proteínas y albúmina, y dichas concentraciones se correlacionan con la exposición. Los experimentos químicos han demostrado que el principal aminoácido al que se unen los anhídridos ácidos cíclicos es la lisina.

La semivida de los anhídridos ácidos cíclicos en la orina humana oscila entre 2 a 3 h para el ácido hexahidroftálico y 14 h para el ácido ftálico. Con el ácido hexahidroftálico se han registrado semividas plasmáticas de 1,7 a 1,8 h.

La dosis letal mediana (LD_{50}) registrada en animales tras exposiciones breves por vía oral, inhalatoria, dérmica o intraperitoneal osciló entre 75,5 y > 15 800 mg/kg de peso corporal. Las menores LD_{50} orales corresponden a los anhídridos ftálico y maleico. Los experimentos realizados en animales han demostrado que el anhídrido maleico y el anhídrido trimelítico son irritantes oculares extremadamente potentes.

En los animales, la exposición a medio plazo ha provocado irritación de los tejidos nasales con hiperplasia y metaplasia. Se ha demostrado que estas alteraciones inflamatorias de los tejidos nasales son efectos reversibles.

Los estudios sobre la exposición a largo plazo o sobre el potencial cancerígeno de los anhídridos ácidos cíclicos en los animales son escasos. Los estudios a largo plazo sobre la administración de anhídrido ftálico a roedores junto con los alimentos no han aportado pruebas de que sea cancerígeno. Se observaron sarcomas subcutáneos en el lugar de inyección en un estudio reducido en el que se inyectó anhídrido succínico por vía subcutánea a ratas.

La base de datos sobre el poder mutágeno y genotóxico de los anhídridos ácidos cíclicos es limitada. La utilización de varios anhídridos ácidos cíclicos en la prueba de Ames con *Salmonella typhimurium* y en ensayos de aberración cromosómica no ha demostrado que tengan poder mutágeno ni que sean genotóxicos.

La base de datos acerca de la toxicidad reproductiva y la toxicidad sobre el desarrollo es muy limitada. Tras la administración de anhídrido maleico a animales durante la gestación no se han observado efectos tóxicos sobre la reproducción ni el desarrollo. En un estudio sobre el desarrollo tras la administración de anhídrido ftálico y anhídrido succínico a ratones se observaron malformaciones en los animales expuestos durante la gestación, pero sólo con dosis que eran tóxicas para las madres. No obstante, este estudio se realizó administrando los compuestos por vía intraperitoneal, una vía de exposición cuya importancia es cuestionable en el ser humano.

Para caracterizar la respuesta y los parámetros inmunitarios, y elucidar el modo de acción de estas sustancias químicas, sus efectos sensibilizadores se han investigado en muchos estudios animales. Varios estudios han concluido que los anhídridos ácidos cíclicos no causan dermatitis de contacto alérgica en los roedores. Los estudios de sensibilización se realizan habitualmente sensibilizando los animales a un anhídrido ácido cíclico y exponiéndolos después a un conjugado del anhídrido con seroalbúmina. Para evaluar las respuestas inmunitarias tras la exposición se han utilizado las concentraciones de anticuerpos y la presencia de focos hemorrágicos pulmonares. Se han observado relaciones dosis-respuesta importantes entre las respuestas inmunitarias y la exposición a los anhídridos ácidos cíclicos. Los anticuerpos que suelen encontrarse aumentados tras la sensibilización y la reexposición son las inmunoglobulinas E y G (IgE e IgG), reactivas frente al conjugado de anhídrido y albúmina estudiado. En ratas sensibilizadas y reexpuestas a anhídrido trimelítico se ha observado

hiperreactividad bronquial y un aumento del número de focos hemorrágicos pulmonares.

Otro enfoque para estudiar los efectos sensibilizadores de los anhídridos ácidos cíclicos consiste en inhibir componentes específicos del sistema inmunitario y la respuesta inmunitaria para comprobar si también se inhibe la sensibilización. En experimentos en los que se ha utilizado el veneno de cobra para inhibir la activación del complemento no se han observado efectos en la broncoconstricción ni las fugas microvasculares inmediatas, aunque la infiltración por células inflamatorias se vio inhibida en el asma inducida por anhídrido trimelítico. Se ha demostrado que la disminución de los macrófagos alveolares inducida por el clodronato alivia la disminución de la función pulmonar inducida por los anhídridos ácidos cíclicos, pero aumenta el daño y la inflamación tisular 24 h después de la exposición.

Los estudios realizados en el ser humano acerca del modo de acción han revelado que los anhídridos ácidos cíclicos producen urticaria y asma alérgica mediadas por la IgE. El asma alérgica va precedida frecuentemente de rinoconjuntivitis mediada por la IgE. Los estudios en animales han demostrado que la histamina y el tromboxano A_2 son responsables de las respuestas boncoconstrictoras temprana y tardía al anhídrido trimelítico. También se ha observado que la exudación en las vías respiratorias es mediada por los leucotrienos y la histamina. Diferentes tratamientos inmuno-depresores han inhibido el aumento de la reactividad de las vías respiratorias, las lesiones pulmonares y las respuestas de anticuerpos a los anhídridos ácidos cíclicos.

En el ser humano, los anhídridos ácidos cíclicos pueden producir irritación y sensibilización tras el contacto directo con la piel y las membranas mucosas, o tras la inhalación. La irritación es causada por el ácido dicarboxílico correspondiente, que se forma cuando los anhídridos ácidos cíclicos reaccionan con el agua. Las enfermedades alérgicas más frecuentes son la rinoconjuntivitis y el asma, ambas de tipo inmediato mediadas por la IgE.

Debido a la naturaleza sensibilizante de los anhídridos ácidos cíclicos, no es posible establecer las concentraciones tolerables según los Criterios de Salud Ambiental (Nº 170). Como orientación para evaluar los riesgos de la exposición a los diversos anhídridos en el lugar de trabajo, se aportan los intervalos de concentraciones que han causado sensibilización y otros efectos con los diversos compuestos a propósito de los cuales existen datos. La menor concentración de cualquiera de los anhídridos ácidos cíclicos que ha causado efectos es de 5 $\mu g/m^3$ (anhídrido metiltetrahidroftálico). En contrapartida, la menor concentración de anhídrido ftálico que causa efectos es de 1500 $\mu g/m^3$.

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