The Nordic Expert Group for Criteria Documentation
of Health Risks from Chemicals and The Dutch Expert
Committee on Occupational Standards

136. Cyclic acid anhydrides

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Preface

An agreement has been 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, which could be used by the national regulatory authorities in both the Netherlands and in 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 has been reviewed by DECOS as well as by NEG.

Editorial work and technical editing was performed by Anna-Karin Alexandrie, and Jill Järnberg, NEG's scientific secretaries at the National Institute for Working Life in Sweden.

All criteria document produced by the Nordic Expert Group may be downloaded from www.nordicexpertgroup.org.

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Abbreviations

Cyclic acid anhydrides

CA	chlorendic anhydride
DSA	dodecenylsuccinic anhydride
HA	himic anhydride
HHPA	hexahydrophthalic anhydride
MA	maleic anhydride
MHHPA	methyl hexahydrophthalic anhydride
MMA	methyl maleic anhydride
MPA	methyl phthalic anhydride
MTHPA	methyl tetrahydrophthalic anhydride
PA	phthalic anhydride
PMDA	pyromellitic dianhydride
SA	succinic anhydride
TBPA	tetrabromophthalic anhydride
TCPA	tetrachlorophthalic anhydride
THPA	tetrahydrophthalic anhydride
TMA	trimellitic anhydride

Other abbreviations

BAL	bronchoalveolar lavage
ECD	electron capture detector
FID	flame ionisation detector
GC	gas chromatography
GPSA	guinea pig serum albumin
HPLC	high performance liquid chromatography
HSA	human serum albumin
MS	mass spectrometry
NIOSH	National Institute of Occupational Safety and Health
PVC	polyvinyl chloride
RSA	rat serum albumin
TLV	threshold limit value
TWA	time weighted average
UV	ultraviolet

Contents

1. Introduction

Cyclic acid anhydrides are widely used in the chemical industry, especially in the manufacture of polyester and alkyd resins and plasticizers for thermoplastic polymers. The anhydrides are also used as hardeners for epoxy resins and chain cross-linkers for thermoplastic polymers. 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 when the paints are burned from surfaces.

Acid anhydrides are irritants and are especially potent as occupational sensitisers.

Phthalic anhydride was the first anhydride to be reported as a sensitiser, as early as 1939. Later several new derivatives were also found to be capable of inducing allergies.

This document deals with the following cyclic organic acid anhydrides: phthalic anhydride (PA), trimellitic anhydride (TMA), maleic anhydride (MA), hexahydrophthalic anhydride (HHPA), methyl hexahydrophthalic anhydride (MHHPA), methyl tetrahydrophthalic anhydride (MTHPA), tetrahydrophthalic anhydride (THPA), and tetrachlorophthalic anhydride (TCPA). Other anhydrides to be mentioned whenever data are available are pyromellitic dianhydride (PMDA), himic anhydride (HA), succinic anhydride (SA), dodecenylsuccinic anhydride (DSA), chlorendic anhydride (CA), and tetrabromophthalic anhydride (TBPA).

This document updates the earlier one given by the Nordic Expert Group in 1991 (101).

2. Substance identification

Data on the substance identification of the cyclic acid anhydrides dealt with in this document are given in Table 1 and Figure 1.

3. Physical and chemical properties

Data on the physical and chemical properties are presented in Tables 2a and 2b. Cyclic anhydrides are mainly powders or crystals. Methyl substitution converts them to oily liquids. A halogen – chlorine or bromine – in the molecule endows flame retardant properties (178).

Table 1. Substance identification of cyclic acid anhydrides (3, 24, 42, 139, 167).

Acid anhydride	CAS No	Synonyms	Molecular formula	Molecular weight
PA	85-44-9	phthalic anhydride 1,3-isobenzofurandione, 1,2-benzenedicarboxylic acid anhydride, phthalic acid anhydride, 1,3-dioxophthalan, 1,3-phthalandione	$C_8H_4O_3$	148.12
TMA	552-30-7	trimellitic anhydride 1,3-dihydro-1,3-dioxo-5-isobenzofuran-carboxylic acid anhydride, trimellitic acid 1,2-anhydride	$C_9H_4O_5$	192.13
MA	108-31-6	maleic anhydride 2,5-furandione, cis-butanedioic anhydride, toxilic anhydride	$C_4H_2O_3$	98.06
HHPA	85-42-7	hexahydrophthalic anhydride 1,2-cyclohexanedicarboxylic anhydride	$C_8H_{10}O_3$	154.17
MHHPA	25550-51-0	methyl hexahydrophthalic anhydride hexahydromethyl-1,3-isobenzofurandione, 4-methylhexahydrophthalic anhydride	$C_9H_{12}O_3$	168.19
MTHPA$_{44}$[a]	26590-20-5	methyl tetrahydrophthalic anhydride 1,2,3,6-tetrahydromethylphthalic anhydride, 3a,4,7,7a-tetrahydromethyl-1,3-isobenzofurane, 4-methyl-delta 4-tetrahydrophthalic anhydride	$C_9H_{10}O_3$	166.19
THPA	85-43-8	tetrahydrophthalic anhydride 4-cyclohexene-1,2-dicarboxylic anhydride, 3a,4,7,7a-tetrahydro-1,3-isobenzofurandione, 1,2,3,6-tetrahydrophthalic anhydride	$C_8H_8O_3$	152.16
TCPA	117-08-8	tetrachlorophthalic anhydride 4,5,6,7-tetrachloro-1,3-isobenzofurandione	$C_8Cl_4O_3$	285.88

[a]4-methyl-delta 4-tetrahydrophthalic anhydride. Commercial products contain also isomers 3-methyl-delta 4-tetrahydrophthalic anhydride (MTHPA$_{34}$) and 4-methyl-delta 3-tetrahydro-phthalic anhydride (MTHPA$_{43}$) (112).
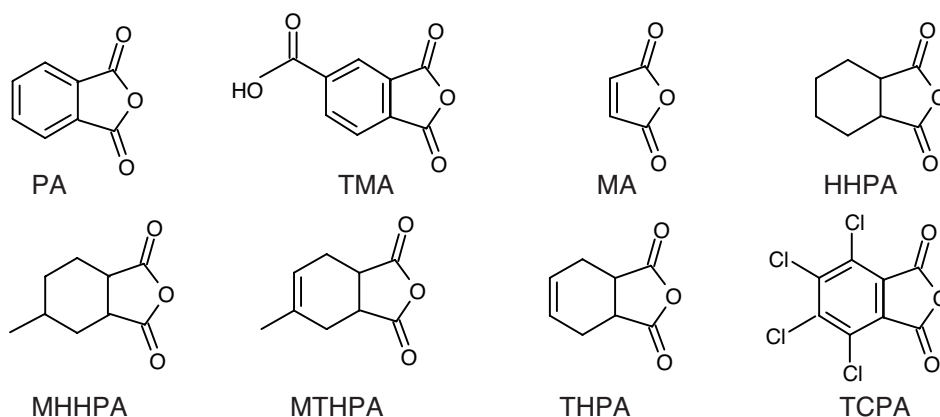
Figure 1. Structural formulas of cyclic acid anhydrides.

Table 2a. Physical and chemical properties of cyclic acid anhydrides (3, 24, 42, 139, 167).

	PA	TMA	MA	HHPA
Description	White crystalline needles	Crystals or needles	Colourless or white crystals, pungent odour	Clear, colourless, viscous liquid
Melting point	130.8°C	161-163.5°C	53°C	Becomes a glassy solid 35-36°C
Boiling point	284°C (sublimes)	240-245°C	202°C (sublimes)	158°C (2.3 kPa)
Vapour pressure (volatility)	<6.6 Pa at 20°C	<10 Pa at 25°C	25 Pa at 20°C	
Vapour density (air=1)	5.1		3.4	
Specific gravity	1.53		1.43 at 20°C	
Density (water=1)	1.53		1.5	1.19 (4°C)
Solubility in water	0.62 g/100 ml		40 g/100ml	
Solubility in organic solvents	Alcohol, ether	Acetone, ethyl acetate, dimethylformamide	Acetone, ethyl acetate, chloroform and benzene	Miscible with benzene, toluene, acetone, carbon tetrachloride, chloroform, ethanol and ethyl acetate. Slightly soluble in petroleum ether
Partition coefficient (octanol/water)	$\log P_{ow}$: -0.62			
Odour threshold	0.32 mg/m^3		1.23 mg/m^3	
Conversion factors in air (25°C, 101.3 kPa)	1 ppm = 6.046 mg/m^3 1 mg /m^3 = 0.165 ppm	1 ppm = 7.842 mg/m^3 1 mg/m^3 = 0.128 ppm	1 ppm = 4.002 mg/m^3 1 mg/m^3 = 0.250 ppm	1 ppm = 6.293 mg/m^3 1 mg/m^3 = 0.159 ppm

Table 2b. Physical and chemical properties of cyclic acid anhydrides (3, 24, 42, 139, 167).

	MHHPA	MTHPA	THPA	TCPA
Description	Oily liquid	Oily liquid	White crystalline powder	White, odourless, free-flowing non hygroscopic powder
Melting point	-29°C		101.9°C	254-255°C
Boiling point	120°C (130 Pa)		195°C (6.7 kPa)	371°C (sublimes)
Vapour pressure (volatility)			1.3 Pa at 20°C	
Vapour density (air=1)			5.25	
Flash point	350°C		157°C	
Density			1.375 (25/20°C)	
Solubility in organic solvents			Slightly soluble in petroleum ether and ethyl ether, soluble in benzene	
Conversion factors in air (25°C, 101.3 kPa)	1 ppm = 6.865 mg/m^3 1 mg/m^3 = 0.146 ppm	1 ppm = 6.783 mg/m^3 1 mg/m^3 = 0.147 ppm	1 ppm = 6.783 mg/m^3 1 mg/m^3 = 0.147 ppm	1 ppm = 11.669 mg/m^3 1 mg/m^3 = 0.086 ppm

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4. Occurrence, production and use

4.1 Occurrence

Organic acid anhydrides are man-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 (183).

4.2 Production

The annual world production of PA has been about 2 200 000 tonnes during the past decade, the European share being about 820 000 tonnes. The main producers in Europe are Belgium, the United Kingdom, the Russian Federation, Italy, and Germany. Of the Scandinavian countries, Sweden has production of PA, about 30 000 tonnes annually. PA production in 1996 was about 830 000 in Asia, about 420 000 in North America and 150 000 tonnes in South America. According to annual export statistics Belgium, the United States and Italy are the main countries to produce MA. The exported amounts were 58 000, 44 000, and 25 000 tonnes, respectively, in 1997 (179).

4.3 Production processes

Industrial processes used in the production of cyclic acid anhydrides are shown in Table 3. Technical anhydride products may contain other related cyclic anhydrides as impurities or they can be mixtures of different isomers. For example, PA contains 0.03% MA and MHHPA contains 4.2% MTHPA (150, 178). The technical product of MTHPA is reported to contain the three isomers 4-methyl-delta 4-tetrahydrophthalic anhydride, 3-methyl-delta 4-tetrahydro-phthalic anhydride, and 4-methyl-delta 3-tetrahydrophthalic anhydride (112).

Table 3. Industrial processes used in the production of cyclic acid anhydrides (24, 178, 217).

Cyclic acid anhydride	Production process
PA	In 1872 by oxidation of naphthalene. After 1960 by oxidation of *o*-xylene. The technical grade product contains 99.9% PA, 0.03% MA, and 0.03% benzoic acid.
TMA	Sublimation of trimellitic acid above its melting point or by heating crude trimellitic acid with vanadium pentoxide.
MA	Catalytic oxidation of benzene or C_4 hydrocarbons.
HHPA	Hydrogenation of THPA.
MHHPA	Hydrogenation of MTHPA.
MTHPA	Diels-Alder reaction between isoprene and MA.
THPA	Diels-Alder reaction between MA and butadiene.
TCPA	Chlorination of PA.

Table 4. Annual import (in tonnes) of acid anhydrides in the Nordic countries and in the Netherlands in 1997 (179).

Acid anhydride	Denmark	Finland	Norway	Sweden	Iceland	The Netherlands
PA	1 263	10 457	–[a]	2 784	–[a]	31 706
MA	–[a]	2 644	5 722	539	–[a]	7 177

[a]Information lacking.

4.4 Use

The information available on the annual import of acid anhydrides in the Nordic countries and in The Netherlands is shown in Table 4. In the trade reports the cyclic acid anhydrides are mainly grouped with related chemicals.

The cyclic acid anhydrides are mainly used in the manufacture of polyester and alkyd resins and plasticizers and as epoxy resin hardeners. The different types of uses for acid anhydrides are presented in Table 5.

5. Occupational exposure data

The concentrations of organic acid anhydrides measured in workplace air are presented in Table 6.

Early measurements of PA showed very high exposure levels (320-17 400 μg/m^3) especially when process difficulties and in loading of reactors occurred (136, 147). When alkyd and unsaturated polyester resins were produced, MA and TMA were used in addition to PA (136).

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 gave 10-100 fold lower concentrations of PA than in the previous studies. The task-specific PA concentrations were higher, up to 1 860 μg/m^3 during charging, giving better information of the peak exposures during the working day. The results of 3 factories were given. In 2 of the factories (factory 1 and 3), TMA and MA were intermittently used in addition to PA and were only detectable in half of the samples (182).

The PA concentrations during polyvinyl chloride (PVC) processing were low, but measurable (180).

Exposure measurements of TMA were carried out during the manufacture of cushioned flooring. The highest exposure levels were in charging (150-20 433 μg/m^3), when both particles and vapours were sampled. Otherwise only few values were above the occupational exposure limit 40 μg/m^3 but the results were based on few samples, 1-4 per task (182).

The exposure levels of MA have been low even in charging in the production of alkyd resins (182).

In two plants for epoxy resin isolation, the highest HHPA concentrations were found in casting (130-500 μg/m^3) based on several personal samples. In one plant

Table 5. Use of organic acid anhydrides (24, 42, 80, 140, 167, 178, 192, 195).

Acid anhydride	Use
PA	Manufacture of phthalate plasticizers, phthaleins, unsaturated polyester resins, alkyd resins, halogenated phthalic anhydrides, and phthalocyanide dyes. Preparation of benzoic acid. Hardener in epoxy resins.
TMA	Manufacture of plasticizers with high thermal resistance and of unsaturated polyester resins. Hardener in epoxy resins.
MA	Manufacture of unsaturated polyesters, alkyd resins, lacquers, plasticizers, co-polymers, lubricants, pesticides, pharmaceuticals, and permanent-press resins (textiles). Synthesis of some organic acid anhydrides. Diels-Alder reaction.
HHPA	Manufacture of alkyd resins, plasticizers, insect repellents, and rust inhibitors. Hardener in epoxy resins.
MHHPA	Hardener in epoxy resins.
MTHPA	Hardener in epoxy resins.
THPA	Production of unsaturated polyester resins and alkyd resins with increased resistance to water and solvents. Starting agent for light coloured alkyds, polyesters, and plasticizers used in adhesives. Intermediate for pesticides. Hardener of epoxy resins.
TCPA	Flame retardant in unsaturated polyester resins, polyurethane foams and surface coatings and plasticizers. Intermediate in the production of dyes and pharmaceuticals. Hardener in epoxy resins.
PMDA	Production of polyimide resins. Polyimide resins are high heat resistant polymers with good electrical and physical properties. They are used for films, fibres, moulding compounds, varnishes, and wire coatings.
HA	Production of fire retardants.
SA	Production of adhesives, dyes, and elastomers. It is used as a cross-linking agent for epoxy resins and as a chemical intermediate for paints containing drying oils, succinylated monoglyceride food emulsifiers, silver haloid photographic emulsions, pharmaceuticals, alkyd resins, and plasticizers.
DSA	DSA is used in alkyd, epoxy and other resins, anticorrosive agents, plasticizers, and wetting agents for bituminous compounds.
CA	Flame retardant in polyester resins and plasticizers.
TBPA	Flame retardant in unsaturated polyester resins and moulding products.

(plant A) also MHHPA was used and exposure levels up to 403 μg/m^3 of MHHPA were found in casting (195). In casting operations in, for example, the electronics industry, solid or semi-solid anhydride curing agents (MTHPA, HHPA and MHHPA) are heated, and the compounds are vaporised (sublimates). The major exposure in these industries may derive from leakages from ovens during the subsequent curing step (195).

When epoxy resin was handled in the wet part of the process in the manufacture of barrels, MTHPA concentrations of 380 μg/m^3 were measured, but exposure levels up to 3 000 μg/m^3 of MTHPA were found close to the heated, wet material before curing (192).

In the manufacture of condensers 5 area samples were collected. The exposure levels of MTHPA in assembling and hardening were between 36.5-695 μg/m^3 (geometric mean). Earlier, before worsening of the work hygiene, 10-fold lower concentrations of MTHPA had been measured (82).

TCPA exposure has been followed in the manufacture of solenoid coils when TCPA cured epoxy resin was used. Exposure levels of 140-590 μg/m^3 were measured in the moulding. After improvements in work hygiene the exposure levels were decreased to <10-110 μg/m^3 (118).

When products containing rest monomers 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, e.g. in the curing of polyester powder paints containing unsaturated polyesters at elevated temperatures. PA has been detected when diethylhexyl phthalate, an ester plasticizer, is heated (147). Cyclic anhydrides have also been detected in welding fumes from painted steel (73, 102).

All cyclic anhydrides react with water, especially if warmed, and the corresponding acid is formed.

When chlorinated anhydrides are heated to the point of decomposition, chlorine is released and toxic vapours are emitted (111).

To conclude, the data on exposure measurements from the workplaces are limited and the measurements have been prompted by work-related health problems at the work place. Mostly the number of samples is small. 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 PA, TCPA, and TMA. The exposure levels from the last decade have generally been lower than the earlier ones 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 sensitising or irritating agents are included in the processes. This makes the exposure more difficult to assess. It is not possible to group cyclic acid anhydrides according to vapour pressure because of lack of data.

Table 6. Exposure measurements of cyclic anhydrides in workplaces.

Acid anhydride / Industry	Processing method/job	No. of samples	Sampling type/time	Results ($\mu g/m^3$)		Method	Reference
PA							
Production of PA and unsaturated polyester resin			Breathing zone/60 min	AM	(range)	Membrane filter, TENAX tube, GC-ECD	(147)
	Flaking	6		1 490	(1 260-1 620)		
	Sacking	6		520	(320-720)		
	Flaking (process difficulties)	4		2 950	(2 340-3 560)		
	Sacking (" ")	4		1 180	(980-1 380)		
Production of alkyd and/or unsaturated polyester resins	*Plant A*		Personal, hours	TWA	(range)	Glass-fibre filter, HPLC	(136)
	Loading of reactors	6	1.9	6 100	(1 800-14 900)		
	Other work	6	12	<0.1			
	Plant B						
	Loading of reactors	18	6.0	6 800	(1 500-17 400)		
PVC processing (incl. di-ethylhexyl phthalate)			Stationary/1.5-3 hours	AM ± SD		Membrane filter, TENAX tube, GC-ECD	(180)
	Extrusion	16		0.3 ± 0.5			
	Calendering	8		0.2 ± 0.1			
	Welding	4		5.0 ± 2.0			
	Injection moulding	2		<0.02			
	Thermoforming	2		0.1 ± 0.05			
	Spread coating	4		1.2 ± 0.2			

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Table 6. Cont.

Acid anhydride Industry	Processing method/job	No. of samples	Sampling type/time	Results ($\mu g/m^3$) AM	GM (GSD)	Method	Reference
PA Production of alkyd resins			Personal/full-shift	AM	GM (GSD)	Glass-fibre filter, TENAX tube, HPLC-UV	(182)
	Factory 1						
	Resin operator	9		25.1	7.6 (4.1)		
	Filter operator	9		1.5	1.2 (1.3)		
	Warehouseman	1		1.0			
	Factory 3						
	Resin operator	12		137.7	9.4 (7.7)		
	Filter operator	3		19.4	9.1 (4.4)		
	Warehouseman	4		4.7	3.2 (2.7)		
	Maintenance	3		3.4	2.8 (2.2)		
	Lab. worker R&D resin	3		15.1	6.4 (8.7)		
	Lab. worker QC resin	4		2.5	1.6 (2.9)		
	Factory 4						
	Resin operator	13		20.1	11.9 (2.9)		
	Pilot plant operator resin	3		10.4	5.3 (4.1)		
	Lab. worker QC resin	10		1.8	1.2 (2.4)		
Production of alkyd resins			Task-specific, min	AM	(range)	Glass-fibre filter, TENAX tube, HPLC-UV	(182)
	Handling bags	2	87.0	33.0	(21.9-44.0)		
	Charging	8	58.6	363.9	(53.8-1 862.6)		
	Sampling/testing	18	78.3	300.3	(8.8-1 276.6)		
	Resin finishing	2	37.0	103.9	(10.6-197.1)		
	Laboratory work	2	91.0	17.5	(5.5-29.5)		
	Opening system	7	15.3	179.6	(6.0-389.3)		
	Delivery of liquid PA	6	38.8	25.0	(6.5-51.4)		

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Table 6. Cont.

Acid anhydride Industry	Processing method/job	No. of samples	Sampling type/time	Results ($\mu g/m^3$)	Method	Reference
TMA						
Manufacture of cushioned flooring			Personal/full-shift	AM	Glass-fibre filter, TENAX tube, HPLC-UV	(182)
	Printer	16		31.2		
	Ink mixer	8		15.4		
	Pilot plant operator flooring	8		3.6		
	De-reel, reel-up operator	10		21.8		
	Floor processing operator	4		5.2		
Manufacture of cushioned flooring			Task-specific, min	AM (range)	Glass-fibre filter, TENAX tube, HPLC-UV	(182)
	Handling bags	1	6.0	99.7		
	Charging	4	15.3	6 340.3 (150.5-20 433)		
	Sampling/testing	2	65.7	4.1 (2.5-5.7)		
	Finishing resin	2	37.0	5.5 (5.1-5.9)		
	Opening system	1	50.0	19.6		
	Clean workplace	1	44.0	60.2		
	Mixing batch	2	21.5	34.0 (16.2-51.7)		
	Mixing inks	3	50.7	19.9 (14.6-26.8)		
	Loading inks	2	26.5	25.0 (17.1-33.0)		
	Printing	2	135.5	12.3 (5.0-19.7)		
	Cleaning equipment	2	26.3	14.3 (11.1-17.5)		

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Table 6. Cont.

Acid anhydride Industry	Processing method/job	No. of samples	Sampling type/time	Results ($\mu g/m^3$)	Method	Reference
MA Production of alkyl resins			Task-specific, min	AM (range)	Glass-fibre filter, TENAX tubes, HPLC-UV	(182)
	Handling bags	1	30.0	6.9		
	Charging	3	13.0	17.3 (10.1-28.6)		
	Sampling/testing	2	83.6	5.5 (1.4-9.7)		
	Finishing resin	2	37.0	10.8 (5.9-15.7)		
HHPA Production of components (A) or capacitors (B), epoxy resin isolation			Personal/sampling rate 0.2-1.0 l/min, 4-55 l air	Mean (range)	XAD-2 tubes, GC-FID	(195)
	Plant A					
	Casting department 1	21		33 (14-131)		
	Casting department 2	18		23 (2-98)		
	Plant B					
	Casting department 1	58		140 (3-470)		
	Casting department 2	13		35 (2-210)		
	Mixed work	7		15 (7-27)		
	Mounting	26		4 (2-9)		
MHHPA Production of components (A)			Personal/sampling rate 0.2-0.1 l/min, 4-55 l air	Mean (range)	XAD-2 tubes, GC-FID	(195)
	Plant A					
	Casting department 1	21		48 (6-403)		
	Casting department 2	18		9 (2-30)		
MTHPA Manufacture of barrels			Personal, hours	GM (range)	XAD-2-tubes, GC-FID	(192)
	Zone I: handling epoxy resin	40	148	85 (7-380)		
	Wet part	32	117	100 (20-380)		
	Dry part	8	31	15 (7-30)		
	Zone II: adj. departments	12	57/personal+area	14 (<1-30)		
	Zone III: other departments	4	17/area	10 (7-14)		

Table 6. Cont.

Acid anhydride Industry	Processing method/job	No. of samples	Sampling type/time	Results (μg/m^3)		Method	Reference
MTHPA							
Manufacture of condensers	*Plant A*		Area/0-60 min, sampling rate 1 l/min.	GM	(GSD)	Silica-gel-tubes (Davisil^{TM}646), GC-ECD	(82)
	Assembly 1	5		36.5	(9.25)		
	Hardening 1	5		129	(3.44)		
	Inspection 1	5		34.2	(6.22)		
	Assembly 2	5		254	(3.06)		
	Hardening 2	5		695	(4.53)		
	Plant B						
	Hardening	5		373	(1.91)		
	Coating	5		185	(3.75)		
	Cutting	5		42.5	(3.80)		
	Finishing	5		4.58	(2.40)		
TCPA							
Manufacturing solenoid coils, TCPA cured epoxy resin	*1989*		Sampling rate 1 l/min	GM	(range)	Teflon filters, TENAX tubes, GC	(118)
	Preformer machine	1	Area	230			
	Moulding	3	Personal	210	(140-340)		
	Moulding	3	Area	320	(170-590)		
	1990						
	Preformer machine	1	Area	30			
	Moulding	6	Personal	21	(<10-110)		
	Moulding	3	Area	9	(<10-10)		
	Leak testing	1	Area	<10			
	Winding	1	Area	10			
	Front office	1	Area	<10			

AM, arithmetic mean; GM, geometric mean; GSD, geometric standard deviation.

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6. Measurements and analysis of workplace exposure

6.1 Measurements and analysis of workplace exposure

Solid sorbent tubes are used for the collection of samples of vapours (Tenax, XAD-2). A bubbler or impinger method is also possible. However, either device will sample the anhydride as the corresponding acid. Therefore a derivatisation step is needed in the analytical procedure. The impinger or bubbler method is also efficient for the sampling of particles but not for small particles formed by, for example, condensed vapour. Another possibility for sampling particles is to use PVC or Teflon filters in series with solid sorbent tubes. To recover both particles and vapours, sampling with both methods is recommended in studies of plants at which the state of the exposure is unknown (87, 93). For analysis, gas chromatography (GC) with flame ionisation detection (FID), electron capture detection (ECD) or mass-spectrometric (MS) detection has been used. Acetic anhydride may be added to the eluting solutions to increase the stability of the samples in the elution and analysis steps (87, 93).

6.1.1 Phthalic anhydride
Pfäffli sampled PA from air with Tenax polymer tubes and analysed PA by GC utilising a ^{63}Ni-ECD. The limit of detection was 0.4 μg/m^3 (0.00007 ppm) with an air sample of 12 1 (147, 149).

PA can also be analysed as the corresponding phthalic acid by reversed phase high performance liquid chromatography (HPLC), as described by Nielsen *et al.* (136).

6.1.2 Trimellitic anhydride
The *Manual of Analytical Methods* published by the National Institute for Occupational Safety and Health (NIOSH) in the United States (US) gives method 5036 for measuring TMA. The air contaminants are sampled on a PVC copolymer membrane filter. After treatment with methanol and boron trifluoride TMA is analysed as its trimethyl ester by GC-FID. The detection limit is 2 μg per sample (400 l air). The method does not differentiate between TMA and trimellitic acid (138).

Geyer *et al.* collected samples on glass fibre filters and converted TMA to the corresponding acid with a 0.05 M NaOH solution. The analysis was carried out with HPLC with an ultraviolet (UV) detector. The minimum quantifiable amount was 1 μg on a filter sample (sample size not given) (55).

Pfäffli modified the NIOSH method using a glass-fibre filter in series with a Tenax tube. The analysis was carried out by GC-ECD. The detection limit was 0.6 μg/m^3 (12 l of air and a sampling rate of 0.2 l/min) (148).

6.1.3 Maleic anhydride
The US NIOSH *Manual of Analytical Methods* gives method 3512 for measuring MA. A known volume of air is drawn through a midget bubbler containing 15 ml

of distilled water. Maleic acid is analysed by HPLC with an UV detector. The limit of detection is estimated to 15 μg/m^3 per sample. The method does not distinguish between MA and maleic acid, and it has limited sample stability (138).

Geyer and Saunders used a similar method with 0.1% phosphoric acid in distilled water as the absorbing solution and as the mobile phase. The minimum quantifiable amount of MA was 100 μg/m^3 of MA using a 100 l air sample (56).

The US Occupational Health and Safety Administration (OSHA) has described an HPLC method for sampling MA, in which sampling is performed on *p*-anisidine-treated XAD-2. Determination of the sampled anhydride using an ECD gave a detection limit of 0.1 μg/m^3 with a 12 l sample volume of air (87).

6.1.4 Hexahydrophthalic anhydride
Jönsson *et al.* reported a method where HHPA was sampled with XAD-2 or a Tenax tube. The analysis was carried out with GC-FID. The detection limit was 0.1 μg/ml of desorption solution (87, 88).

HHPA has also been sampled with bubblers containing aqueous sodium hydroxide (NaOH) and detected using GC with FID or electron ionisation MS after derivatisation to dimethyl esters. The detection limit using electron ionisation MS was 0.01 μg/sample (60 l of air) (87, 88, 93).

Glass-fibre filter sampling (eluted with aqueous NaOH, derivatisation with pentafluorobenzyl bromide and determination by GC-MS in the negative-ion chemical ionisation mode gave results comparable with those of the Tenax method (93).

A Fourier transform infrared spectrometer has been tested for the direct measurement of peak levels of HHPA. The limit of detection was 120 μg/m^3 (117).

6.1.5 Methyl hexahydrophthalic anhydride
MHHPA has been sampled with Tenax tubes and analysed with GC-ECD (151). When the sampling was carried out with XAD-2 tubes and analysed with GC-FID, the detection limit was 0.1 μg/sample (sample volume not given). The detection limit was equal for the *cis* and *trans* isomers of MHHPA (93).

6.1.6 Methyl tetrahydrophthalic anhydride
MTHPA has been sampled using Amberlite XAD-2 solid sorbent tubes and analysed by GC-FID. The detection limit for air samples was 10 μg/m^3 for a 20 l sampling volume (189). The sensitivity was equal for the isomers in technical quality of MTHPA (112).

Johyama *et al.* used silica-gel tubes for the sampling and GC-ECD for the analysis. MTHPA concentrations >1.0 μg/m^3 were quantified at 20 minutes sampling with a sampling rate of 1 l/min (82).

6.1.7 Tetrahydrophthalic anhydride
THPA has been sampled with XAD-2 tubes and analysed using GC-FID. The detection limit was 0.1 μg/sample (sample volume not given) (93).

6.1.8 Tetrachlorophthalic anhydride
Liss *et al.* sampled TCPA with Teflon filters connected to Tenax tubes and made the analysis using GC. No detection limits were given (118).

6.2 Measurements of dicarboxylic acids from samples of urine and plasma

Pfäffli reported a method for determining the dicarboxylic acids of PA, HHPA, MHHPA, and THPA in urine. The acids were esterified with 2,2,2-trichloro-ethanol 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 (151). In another study by Pfäffli urine samples were collected from PA exposed workers pre-shift, on-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 detection limit was 0.05 μmol/l (10 ml urine samples). A significant correlation was found between the phthalic acid concentration in urine samples and the atmospheric PA concentrations. When the exposure level was about 30% of the hygienic reference value at that time 6 000 μg/m^3, a body-burden was caused which was not eliminated overnight (146).

Jönsson *et al.* used esterification with methanol and boron trifluoride and GC-MS for the analysis. For HHPA-exposed workers a correlation was found between time-weighted levels of HHPA in air and hexahydrophthalic acid in post-shift urine (r_s=0.93; p<0.023). The detection limit in urine was 20 ng/ml. Because the urine analysis of one worker exposed to a HHPA time weighted average (TWA) concentration of 30 μg/m^3 showed that more than 85% of the inhaled amount was excreted in the urine as hexahydrophthalic acid, it was estimated that it is possible to monitor HHPA air concentrations of approximately 1-2 μg/m^3 with this method (86, 89).

Lindh *et al.* developed the method further for the analysis of methyl tetrahydro-phthalic acid in urine. The commercial MTHPA used was composed of three major isomers. The overall detection limit for the three isomers was <6 ng/ml (112).

The method was further developed to be less labour-intensive in biological monitoring and applicable for the determination of hexahydrophthalic acid and methyl hexahydrophthalic acid. The detection limits in urine were 11 ng/ml and 17 ng/ml, respectively (84).

A method has been developed to measure hexahydrophthalic acid and methyl hexahydrophthalic acid simultaneously in plasma. Pentafluorobenzyl bromide was used as the derivatisation agent and the pentafluorobenzyl esters formed were analysed by GC-MS. The detection limit was 0.4 ng/ml for hexahydrophthalic acid and 0.3 ng/ml for methyl hexahydrophthalic acid (113).

6.3 Conclusions

Sensitive methods are available to measure air levels of exposure to cyclic acid anhydrides at the workplace. It is important to choose sampling method according

to the type of exposure. There are also sensitive methods for analysing the corresponding dicarboxylic acids to PA, HHPA, MHHPA, MTHPA, and THPA in urine, and dicarboxylic acids in plasma originating from HHPA and MHHPA.

7. Toxicokinetics

7.1 Uptake

When 5 healthy volunteers were exposed to gaseous HHPA at 80 μg/m^3 for 8 hours, 1-4% was found in exhaled air during exposure. The concentration of the metabolite hexahydrophthalic acid in plasma rose rapidly during exposure (90). One worker was exposed to an 8 hour TWA concentration of HHPA of 30 μg/m^3 and urine was collected during 24 hours. More than 85% of the inhaled dose was excreted in urine as hexahydrophthalic acid (86).

HHPA (1 400 μg) in petrolatum was applied with the epicutaneous skin test technique (4 Finn Chambers) to the back skin of 3 volunteers for 48 hours. The volunteers´ urine was collected for 72 hours. The excreted amounts of hexahydrophthalic acid, as a fraction of the totally applied amount of HHPA, were within intervals between 1.4-4.5%, 0.2-1.3% and 0-0.4%, respectively for the 3 subjects. This indicated that the percutaneous absorption of HHPA was minimal. The person with the highest absorption had pale erythema after the removal of the mixture from the skin, a possible higher absorption through inflamed skin was suggested (91).

There are no data on absorption via the gastrointestinal system.

In conclusion, absorption of HHPA via inhalation is efficient whereas dermal absorption is low.

7.2 Distribution

Lindh *et al.* studied the distribution of HHPA by autoradiography after exposing guinea pigs and rats to (^{3}H$_2$)HHPA via inhalation for 3-8 hours. Medium to high levels of radioactivity were found in the mucosa of the nasal region and trachea, whereas negligible levels were observed in lung tissue. Tissue-bound radioactivity was also present in the gastrointestinal tract and conjunctiva. A low level of tissue-bound radioactivity was found in the cortex of the kidneys in rat, but not in guinea pigs. The radioactivity persisted for at least 7 days after the end of the exposure. The HHPA-derived radioactivity could only partially be extracted by organic solvents and water, suggesting a covalent binding to tissue macromolecules. However, in the lung, the little radioactive HHPA that was found could also be extracted. The radioactivity in dialysed plasma was mainly found in the same fractions as albumin (115).

7.3 Biotransformation and excretion

Acid anhydrides are used to change the properties of proteins to separate them from their matrix (141). The anhydride group reacts readily with amino acids and this reaction explains their conjugation with human serum albumin (HSA), which takes place in the hapten formation of acid anhydrides (175, 214). TMA was conjugated with HSA rapidly *in vitro* at 37°C. The reaction was essentially completed in 1 minute (214).

Plasma protein and albumin adducts have been measured in sera from HHPA- and MHHPA-exposed workers. The adduct levels correlated well with the exposure. The half-time of the adducts *in vivo* was about 20 days (161).

MTHPA was mainly bound to lysine in the collagen of guinea pig lung in both *in vitro* and *in vivo* exposure tests (92). When human erythrocytes were exposed to HHPA and MHHPA, conjugation with haemoglobin was found. The major amino acid binding HHPA was also lysine (114).

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

Both in an animal study and when MHHPA-exposed workers were investigated, it was shown that the hydrolysis of the anhydride in the body takes time (150, 166). MHHPA concentrations from 3.4-10.7 nmol/l were detectable after the work-shift in the blood samples of workers exposed to MHHPA at levels between 140-310 μg/m^3. The MHHPA found had the same *cis* form as in the air samples. No free acids were found (150).

Pfäffli followed the excretion of phthalic acid in workers exposed to PA by taking urine samples pre-shift, on-shift, post-shift, in the evening, and on the following morning. At low atmospheric exposure to PA (150 (range 30-330) μg/m^3) the pre-shift phthalic acid concentrations were on the same level as those found in the urine samples of occupationally unexposed people (0.34 (range 0.02-0.89) μmol/mmol creatinine). In workers exposed to higher concentrations (1 630 (standard deviation (SD) 130) μg/m^3 of PA) an accumulation of phthalic acid in urine was found. The pre-shift phthalic acid excretion was 1.02 (SD 0.25) μmol/mmol creatinine. When the exposure was high, 10 500 μg/m^3, the pre-shift urinary concentration was 4.8 μmol/mmol creatinine, about 14 times that seen in workers with low exposure. No conjugation of phthalic acid to glucuronide was observed (146).

The urine analysis of one worker exposed to a HHPA concentration of 30 μg/m^3 (TWA) showed that more than 85% of the inhaled amount was excreted in the urine as hexahydrophthalic acid (86).

The half-time of phthalic acid in urine of PA-exposed workers was shown to be about 14 hours (146). The assumed half-time of the dicarboxylic acids in the urine of workers with low exposure to MHHPA was about 7 hours, and for HHPA and THPA the corresponding value was about 14 hours. After 4 hours of exposure to an MHHPA concentration of 116 μg/m^3 in air, an input-output equilibrium for the anhydride and the urinary acid developed (151). In another study the half-time of hexahydrophthalic acid in urine was 2-3 hours in HHPA-exposed workers (86).

The half-times of hexahydrophthalic acid in plasma of 2 male healthy volunteers were 1.7-1.8 hour after exposure to 80 μg/m^3 HHPA for 8 hours (90). Urine analysis indicated half-times of 3, 3 and 6 hours for the three isomers 3-methyl-delta 4-tetrahydrophthalic anhydride, 4-methyl-delta 4-tetrahydrophthalic anhydride, and 4-methyl-delta 3-tetrahydrophthalic anhydride, respectively in a worker exposed to commercial MTHPA (112).

To conclude, cyclic acid anhydrides bind to plasma proteins and haemoglobin. The main binding amino acid seems to be lysine. The half-time of MHHPA-adducts has been shown to be 20 days. Cyclic acid anhydrides are after hydrolysation to corresponding dicarboxylic acids effectively excreted in urine. As much as 85% of the inhaled dose of HHPA has been recovered in urine. The half-time for the dicarboxylic acid of PA in urine was 14 hours, whereas the corresponding half-times of HHPA, MHHPA and MTHPA were in general shorter, between 2 and 7 hours.

8. Biological monitoring

Pfäffli analysed phthalic acid in urine of workers exposed to PA levels of 30-10 500 μg/m^3 (TWA) and found concentrations between 0.3-14.0 μmol/mmol creatinine. At exposure levels of 2 000 μg/m^3 of PA, phthalic acid could still be detected in urine the next day (146).

Hexahydrophthalic acid in plasma and in urine of experimentally exposed volunteers showed good correlation (r>0.90) with the air level of HHPA (90).

In another experiment the researchers studied 27 workers exposed to a mean MHHPA concentration of 15 (range 5-60) μg/m^3, mainly in casting and in leaks from curing ovens in a plant manufacturing electrical capacitors. Urine was collected during the last 4 hours of the shift and from 8 workers before the start of the work shift and then at 4-hour intervals (7 hours during the night) for 24 hours. Plasma was sampled at the end of the 8-hour work shift. The elimination half-time in urine varied between 4 and 10 hours. Workers exposed to less than 10 μg/m^3 had urinary levels below the quantification limit before the next shift. A correlation (r=0.94) was found between the TWA air levels of MHHPA and the creatinine-adjusted methyl hexahydrophthalic acid levels in urine samples collected during the last 4 hours of the exposure and likewise between the exposure and the plasma concentration of methyl hexahydrophthalic acid. An exposure to 20 μg/m^3 corresponded to a methyl hexahydrophthalic acid concentration of about 140 nmol/mmol creatinine in urine and about 40 nmol/l in plasma (116).

When protein adducts were measured in the plasma of HHPA and MHHPA exposed workers, the concentrations correlated with the exposure levels. It was shown that air levels even below 1 μg/m^3 of HHPA and MHHPA were possible to monitor (161).

In cross-sectional studies the proportion of persons with immunoglobulin (Ig)G specific for PA, HHPA and MTHPA increased as exposure increased (136, 192,

195). However, as 50% or more of the subjects were negative even in the groups with the highest exposure intensity, the value of IgG as a biomarker of exposure seems limited. This limitation is emphasised by the results of Jönsson *et al.* who measured both haemoglobin adducts and HHPA-specific IgG antibodies in serum in HHPA exposed workers. The exposure was determined from the analysis of urinary carboxylic acid measurements. The authors found a correlation (r=0.87) between the urinary hexahydrophthalic acid level and the number of haemoglobin-HHPA adducts. However, there was no significant correlation between the exposure and the HHPA-specific IgG (85).

In conclusion, measurement of the corresponding dicarboxylic acids in the urine of exposed workers is a sensitive non-invasive method for biological monitoring of some cyclic acid anhydrides. Measurement in plasma samples is also possible. However, biomonitoring data and methods to measure the corresponding acids of TMA, MA and TCPA are lacking.

The determination of specific IgG antibodies from blood samples does not give information of the exposure level according to studies on HHPA-exposed workers. Results obtained with determination of protein adducts (HHPA and MHHPA) in plasma are more promising.

9. Mechanism of toxicity

9.1 Irritation

Cyclic acid anhydrides react easily with water, and the corresponding acids are formed. The formation of acids explains the irritating effects on the skin and the mucous membranes of the eyes and the respiratory organs (11, 15, 23, 45, 47, 122, 136, 171).

9.2 Allergic contact dermatitis (Type IV)

In animal studies PA has been classified as a moderate sensitiser causing allergic contact dermatitis of type IV allergy (48). When the allergenicity of chemicals was more recently studied using cytokine stimulation, PA, TMA, MA, HHPA and MTHPA were not considered as contact allergens (31-33). The small number of case reports also suggests that the potency of cyclic acid anhydrides to induce allergic contact dermatitis is low (94, 96).

9.3 Contact urticaria (Type I)

IgE-mediated contact urticaria due to cyclic acid anhydrides is more usual. MHHPA, MTHPA, HHPA, CA, and MA have induced contact urticaria in exposed workers with specific IgE antibodies and positive results in skin prick tests and in open tests with the anhydride (83, 94, 95, 102, 174). In some cases airborne exposure without skin contact has resulted in contact urticaria (95, 174).

9.4 Respiratory sensitisation

Allergic asthma, often preceded by rhinoconjunctivitis, is a well documented disease of workers exposed to cyclic acid anhydrides, and its occurrence has stimulated several works concerning the mechanism of the sensitisation. In case reports and industrial surveys, IgE mediated sensitisation has been verified by positive reactions in skin prick tests with conjugates of the anhydrides and HSA, and by specific IgE. In exposed workers, bronchial hyperresponsiveness, a typical finding in asthma, has been correlated to the specific sensitisation (14). Immediate, dual, or late bronchial reactions have been found in challenge tests with PA, MA, HHPA, MTHPA, TCPA, and PMDA (16, 17, 26, 36, 37, 108, 168, 184, 186, 196).

The formation of protein adducts *in vivo* is believed to be the first step in the sensitisation process. This has been shown when total protein and albumin adducts of HHPA and MHHPA were measured in the plasma of exposed workers (161).

Also in sensitised animals the formation of anhydride-specific IgE and IgG antibodies has been shown (4, 10, 68, 71, 217, 219, 220). In studies with PA, TMA, and HHPA, an obstructive bronchial reaction has followed the challenge tests of sensitised animals (10, 28, 68, 71, 165, 218).

There are some findings of mediator release in acid anhydride sensitivity. When basophilic leukocytes were challenged *in vitro* with PA or TCPA-HSA conjugates, there was a release of histamine, a mediator of allergic reaction. The *in vitro* histamine assay was claimed to be useful in the identification of subjects with allergic responses to anhydrides, even without evidence of IgE-mediated reaction (44).

In animal studies using pretreatment with different blocking agents, the mediators histamine and thromboxane A_2 have been shown to be mainly responsible for the early and late bronchoconstriction response to TMA. Leukotrienes and histamine were found to mediate airway plasma exudation to some extent (6, 8, 69, 71). In sensitised guinea pigs, pretreatment with budesonide signifycantly inhibited the increase in airway responsiveness, but not the eosinophilic inflammation, induced by exposure to TMA dust (67).

Rats pretreated with the immunosuppressant cyclophosphamide showed no lung lesions and no antibody reaction after exposure to 95 μg/m^3 TMA 6 hours/day, 5 days/week for 2 weeks. Thus, the elimination of T- and B-lymphocyte function could prevent the TMA-induced lesions (106).

Oral pretreatment with cyclosporin A inhibited the immunisation process caused by TMA in guinea pigs, whereas betamethasone and azelastine had no significant effect (5). In another study with brown Norway rats both betamethasone and cyclosporin A given over the time of sensitisation inhibited the development of TMA specific IgE and IgG (155).

Activation of inducible nitric oxide synthase has been demonstrated in bronchial tissue after TMA-guinea pig serum albumin (GPSA) challenge in sensitised guinea pigs (198).

The pulmonary disease-anaemia syndrome described due to fumes from TMA-cured epoxy resin, is a rare disease with haemorrhagic alveolitis and specific IgG antibodies. In animal studies similar reactions have been found (25, 107).

9.5 Conclusion

Cyclic acid anhydrides are irritants because of formation of corresponding acids in wet surroundings. They rarely induce contact allergy of the skin but more easily induce IgE-mediated contact urticaria. The mechanism of respiratory sensitisation is mainly IgE mediated allergy both in animal studies and when exposed workers have been investigated. In the challenge tests bronchial obstruction has been verified, as well as development of inflammation. The determination of specific antibodies and mediators of allergies and allergic inflammation in the studies with cyclic acid anhydrides has given new information on allergic reactions in general.

10. Effects in animals and *in vitro* studies

10.1 Irritation and sensitisation

10.1.1 Irritation
In animal studies PA has not been found to be as irritating as MA and TMA (Table 7).

A PA solution (50%) in oil did not irritate rabbit ears after 20 hours of exposure (34). PA (0.5 g/patch) did not cause skin irritation on rabbits when applied by the semi-occlusive or occlusive method over a period of 1 or 4 hours. The results were assessed at 1, 24, 48 and 72 hours, or 7 days later (154).

One drop of PA (5%) in polyethylene glycol 400 was slightly irritating to rabbit eyes, while a 0.5% solution was not irritating (34). In an experiment with rabbits, the irritant effects of PA on the skin and eyes correlated with each other. PA was found to be a mild skin irritant, but a moderate eye irritant (47).

TMA (50%) caused dermatitis in mice and rats after a single or repeated application to the skin for 2 hours. The effects were slight and reversible (15).

MA and TMA have been shown to be extremely irritating to eyes in animal experiments. There was cloudiness of the cornea and hyperaemia of the conjunctiva a few minutes after the application of 1% MA to the eyes of rabbits. The next morning the eyes were normal. A 5% solution of MA induced more intense irritation, which lasted 1 week. A minute amount of MA powder caused long-lasting damage with vascularisation of the cornea of the rabbit (197). The application of 50 mg of TMA powder to rabbit eyes produced reversible hyperaemia of the conjunctiva, and lacrimation and blepharospasms (15).

In a 6-month inhalation study on MA, rats, hamsters and monkeys were exposed to concentrations of 0, 1 100, 3 300, and 9 800 μg/m^3, 6 hours/day for 5 days/week. Dose-related ocular and nasal irritative signs were present at all

Table 7. Irritative and sensitising effects of acid anhydrides on different animal species.

Anhydride/ Species	Route of administration	Exposure data	Effect	Reference
PA				
Rabbit	Eye application	50 mg	Moderate irritation	(139)
Rabbit	Dermal (patch)	500 mg (1 or 4 h)	No skin irritation	(154)
Rat, Brown Norway	Intradermal	0.1 ml 0.2 M PA[a]	Specific IgE and specific IgG antibodies	(220)
TMA				
Rabbit	Eye application	50 mg	Conjunctival hyperemia, lacrimation	(15)
Guinea pig	Intradermal	0.1 ml of 30% TMA	Specific IgG_1 and IgE antibodies	(22)

[a] Specific IgE and IgG antibodies have been induced in similar studies with TMA, MA, HHPA, MHHPA and MTHPA (220).

exposure levels. A histopathological examination of nasal tissue (turbinate sections immediately posterior to the upper incisors) revealed irritation (hyperplasia, metaplasia) in rodent species and inflammatory changes in all species. All changes were judged to be reversible (171).

10.1.2 Allergic contact dermatitis
The potency of PA to induce allergic contact dermatitis has been investigated with the Buehler test (closed patch test in guinea pigs) and the mouse ear swelling test (MEST). According to both tests PA was classified as a moderate sensitiser (48). The guinea pig maximisation test has not been carried out with acid anhydrides.

In other studies investigating the patterns in cytokine production following topical sensitisation, PA, TMA, MA, HHPA and MTHPA were not found to be contact allergens (31-33).

10.1.3 Respiratory sensitisation
Table 8 contains data from the respiratory sensitisation studies. Sensitisation with the production of specific antibodies is essential for the development of an allergic respiratory disease. Antibody response has been induced by both bronchial, subcutaneous, intradermal and parenteral sensitisation routes.

When monkeys were exposed parenterally to PA-monkey serum albumin (MSA), PA dissolved in ethanol saline, MSA, or ethanol-saline alone, sensitisation was observed only with PA-MSA. The presence of new antigenic determinants formed by PA on protein carriers was essential for the parenteral sensitisation (21).

Guinea pigs were sensitised by inhalation of PA dust at 500, 1 000, 5 000 μg/m^3, for 3 hours/day for 5 consecutive days. A PA-guinea pig serum albumin (GPSA) challenge after 2 weeks elicited an immediate onset of respiratory reactions, determined by plethysmography, in animals exposed to all 3 levels of dust. The inhalation challenge with PA dust (5 000 μg/m^3) did not cause an

immediate response, but the animals had significant number of haemorrhagic lung foci. No foci were seen in the lungs of PA-GPSA challenged animals. IgG-PA-GPSA antibodies were detected in sera of all the PA-exposed animals, and the dose-response relationship was highly significant (165).

In a Japanese study rabbits were sensitised subcutaneously to PA-rat serum albumin (RSA). High titres of IgG against PA-RSA were found, but also against PA-HSA and HSA. IgG-PA-HSA antibodies had cross-reactivity with HHPA-HSA, MHHPA-HSA, and MTHPA-HSA. After purification of specific IgG-PA, the levels of specific IgG to other conjugates were unchanged. Two types of IgG antibody production were suspected, one to PA hapten alone and the other to new antigenic determinants on HSA (66).

Dykewicz *et al.* sensitised 2 rhesus monkeys intrabronchially with serum from a worker with TMA asthma and high titres of IgE, IgG, and IgA to TMA-HSA. The monkeys were challenged with TMA-HSA aerosol and bronchospasm appeared. After 1 week the challenge was negative. Passive cutaneous anaphylaxis was also found with the Prausnitz-Küstner test (38).

In an inhalation experiment rats were exposed 3 hours/day for 5 days to 0, 10, 30, 100 or 300 μg/m^3 of TMA dust. Haemorrhagic lung foci were found in relation to exposure concentrations of 30-300 μg/m^3. The serum antibody binding of trimellitic-RSA correlated with exposure concentration, presence of haemorrhagic lung foci and lung weight. The lung lesions had healed 12 days after the exposure, but returned soon after a repeated exposure (211). A histological examination of the lung lesions indicated extensive cellular infiltration, primarily macrophages, alveolar haemorrhage, and pneumonitis. These effects increased in proportion to the concentration. The lungs were the only organs affected (107).

Chandler *et al.* exposed rats to TMA powder (100 μg/m^3) for 6 hours/day, 5 days/week for 2 weeks. Haemorrhagic foci were observed on the surface of the lungs at autopsy. The authors found higher total antibody concentrations in the fluid of bronchoalveolar lavage (BAL) than in serum. IgG, IgA, and IgM antibodies to TMA-RSA were detected. Inhibition studies showed that both TMA-RSA and TMA-HSA conjugates cause complete inhibition of the rat IgG binding, whereas the human IgG was inhibited only by TMA-HSA. The early antibody response in the rat was directed towards new antigenic determinants common to TMA-modified albumins (25). The immune response to inhaled TMA has been found to occur in parallel with the development of lung lesions. The antibody levels in BAL and serum were highly correlated with the lung injury (209).

After rats had inhaled TMA powder (500 μg/m^3 or 330 μg/m^3) on days 1, 5 and 10 for 6 hours/day they were challenged with TMA (540 μg/m^3 or 300 μg/m^3), on day 29 or 22, respectively. In the high exposure group, IgM and IgA antibodies to TMA-RSA started to increase from day 5 and peaked at day 20. IgG antibodies appeared on day 7 and peaked at day 20. A mean of 216 haemorrhagic lung foci was found. In the low exposure group animals that were not rechallenged had fewer lung foci than the rechallenged animals. In the rechallenged group there was a correlation between all the antibody measures and lung injury. A subgroup of animals was exposed to a TMA level of 500 μg/m^3 only on days 1 and 5 and

challenged with 500 μg/m^3, on day 29. A mean of 112 haemorrhagic lung foci was found, and there was a good correlation between the antibody response and the lung injury (208).

Hayes *et al.* developed a guinea pig model for TMA-induced airway hypersensitivity responses by sensitising animals intradermally with 0.1 ml of 0.3% free TMA in corn oil. Control animals were given 0.1 ml corn oil. An increase in the level of specific serum IgG$_1$ antibodies was found in all sensitised animals, and IgE antibodies were detected in 6 of 8 sensitised animals. On days 21 to 28 a tracheal challenge (50 μl) with 1% TMA-GPSA gave increased lung resistance in sensitised animals compared with non-sensitised animals. Airway microvascular leakage was also seen in sensitised animals when tested with Evans blue (70). When challenged by inhalation through the nose (12 000 μg/m^3 TMA, 30 minutes), the animals showed a significant increase in bronchial reactivity 8 hours after the exposure, and the increase was accompanied by an eosinophilic inflammatory exudate (68).

Arakawa *et al.* investigated the time course of immune and airway responses after sensitising guinea pigs through two intradermal injections (0.1 ml of 0.3% TMA in corn oil). They challenged the animals after 1, 2, 3, 5 and 8 weeks with 50 μl of 0.5% TMA-GPSA intratracheally. The challenge induced a significant increase in lung resistance, reaching a maximum at 2.5 minutes in the 1-week group and between 5 and 6 minutes in the other sensitised animals. A significant extravasation was also found that increased up to 8 weeks. Specific IgG$_1$ antibodies were detected in all the animals in the 3-, 5-, and 8-week groups; this result correlated with the extravasation but not with the increase in the resistance (7).

Brown Norway rats were intradermally sensitised with TMA and then challenged once or seven times with TMA-RSA conjugate. High levels of TMA-specific IgE and IgG were found in all the sensitised rats when they were compared with controls. A single allergen challenge did not cause bronchial hyperreactivity but repeated challenge produced significant bronchial hyperreactivity in sensitised rats. Repeated, low-dose challenges produced more hyperreactivity than a 10 times higher single dose. Bronchial eosinophilia was found in the sensitised and single-challenged groups, but not in the non-sensitised non-challenged and sensitised re-challenged groups (28).

Inhibiting complement activation prevented inflammatory cell infiltration in TMA-induced asthma. This phenomenon was studied by pretreatment of guinea pigs with a cobra venom that reduced the complement component C$_3$ in broncho-alveolar lavage fluid after TMA-GPSA challenge. The immediate bronchoconstriction was not affected, nor was the microvascular leakage. The TMA-induced increase in mononuclear cells, total white blood cells and red blood cells, and the erythrocyte peroxidase activity was reduced (46).

When sensitised brown Norway rats were challenged, TMA induced an immediate bronchoconstriction. Eosinophilic aggregates and goblet cell hyperplasia and hypertrophy were seen in the lungs and also induction of haemorrhages in

sensitised animals. A less marked eosinophilic infiltration of the lungs was seen also after the challenge tests of the non-sensitised animals (10).

Zhang *et al.* studied the mechanism of allergy by developing a regime for the intradermal sensitisation of guinea pigs to HHPA. The animals were immunised by an intradermal injection with single and booster injections of 0.1 ml of 0.02%, 0.1%, 0.5%, 5%, and 10% mixtures of HHPA in olive oil. Single injections of <0.5% produced no positive findings of specific IgE or IgG antibodies. A single injection induced optimal levels of IgG after 14 days at a dose of 5% HHPA. The IgE titres were low and only positive in 40-50% of the animals at injections of 0.5-10% HHPA. For IgE induction, booster injections were needed (217). The authors also studied the relationship between specific IgG_1 levels and airway responses to predict the sensitising potential of acid anhydrides. They concluded that allergen challenge in HHPA-sensitised guinea pigs results in both airway obstruction and plasma extravasation, and that responses are related to the serum levels of specific IgG_1 (218, 219).

Anaphylactic bronchoconstriction has been induced in guinea pigs sensitised with HHPA or MTHPA and challenged by inhalation or intravenously with the corresponding GPSA conjugate. A steep dose-response relationship was found. The critical dose was accordingly established to be approximately 40 μg/kg (221).

A model to differentiate chemicals for different types of allergenicity has been developed. Mice were sensitised topically, by applying the test material dissolved in 4:1 acetone:olive oil, to a shaved flank under an occluded patch for 48 hours. After 5 days the ear thickness was measured, and then the dorsum of both ears was treated with 25 μl of the tested chemicals, TMA, and 2,4-dinitrochloro-benzene, the later being a potent contact allergen without respiratory sensitisation properties. When the levels of activation (cell proliferation) in lymph nodes draining the site of application were similar, comparable levels of contact sensitisation and IgG anti-hapten antibodies were induced by these chemicals, but only TMA increased the IgE production. Furthermore, while TMA induced IgG_{2b} rather than IgG_{2a} antibodies, the reverse pattern was observed with the contact allergen. The results pointed to a different type of T lymphocyte (Th_1 and Th_2) response to these chemicals (31). A similar response has been found with PA, MA, HHPA, and MTHPA (32, 33). Arts *et al.* used brown Norway rats in a very similar setting with TMA, dinitrochlorobenzene, formaldehyde, and methyl salicylate. They also found a significant increase in the serum IgE concentration after exposure to TMA but not after exposure to the other chemicals, skin sensitisers, or irritants (9).

Welinder *et al.* studied the relationships between chemical structure and immunogenicity for 13 dicarboxylic acid anhydrides in guinea pigs intra-dermally sensitised with SA, MA, methyl maleic anhydride (MMA), *cis*-HHPA, *trans*-HHPA, MHHPA, *cis*-1,2,3,6-tetrahydrophthalic anhydride ($THPA_{1236}$), *cis*-3,4,5,6-tetrahydrophthalic anhydride ($THPA_{3456}$), $MTHPA_{34}$, $MTHPA_{44}$, PA, 4-methyl phthalic anhydride (4-MPA) and TMA. Specific IgG was significantly increased in all animals except those immunised with $THPA_{3456}$ and SA, which sensitised some but not all the animals. The titres of specific IgG_1 and IgG_2 were

increased in IgG-positive animals. Passive cutaneous anaphylaxis test was used for determining specific IgE. Specific IgE was positive in all the animals immunised with MA, MHHPA, MTHPA (both isomers), and 4-MPA and in 6/9 and 5/9 guinea pigs immunised with TMA and MMA, respectively. The test results were contradictory for PA and HHPA. The sensitising potentials of different organic acid anhydrides showed a considerable variation. The substitution of hydrogen in the C_4 position by a methyl group or adding a double-bond to the same position enhanced the immunogenicity of the anhydrides (194, 219). In brown Norway rats sensitised intradermally with 14 different acid anhydrides (0.1 ml of 0.2 M) or 3 anhydride conjugates (1 400 μg of RSA conjugate) specific IgE antibodies were measured after 4 weeks. The titres (median) obtained after sensitisation with free MPA, PA, *cis*-HHPA, 4-MHHPA and TMA were 1 600-3 200 (range 800-6 400) and after sensitisation with MA, THPA$_{1236}$ and both isomers of MTHPA the titre was 800 (range 200-3 200). SA as free was negative, but in conjugate form, positive titres of specific IgE were found as well as with MA and *cis*-HHPA conjugates (220).

The specificity of the antibodies was studied with inhibition tests. The anhydrides with methyl group or double-bond similar to the sensitising anhydride caused higher inhibition effect when compared to the anhydrides with different structures (217, 219, 220).

In conclusion, specific IgE and specific IgG antibodies (PA, TMA, HHPA, MHHPA, and MTHPA) have been measured as a marker of sensitisation in animals after immunisation. In guinea pig studies methylation and the presence of a double bonding in the C_4 position of the anhydride molecule enhanced the sensitising potential. However, the results of the studies with brown Norway rats were partly different. In inhibition studies cross-reactivity was shown between anhydrides with similar structures. In challenge studies of sensitised animals, bronchial responses similar to bronchial asthma in humans have been seen. TMA dust evokes a lung reaction in animals that is similar to the pulmonary disease-anaemia syndrome.

Table 8. Effects of acid anhydrides on animals in short-term exposure studies concerning sensitisation.

Anhydride/ Species	Route of administration	Exposure data	Effect	Reference
PA				
Guinea pig	Inhalation	500, 1 000, 5 000 $\mu g/m^3$ PA dust 3 h/day for 5 days, challenged with PA-GPSA 2 000 $\mu g/m^3$ or PA dust 5 000 $\mu g/m^3$	IgG antibodies in lowest exposure greater than in air exposure ($p<0.05$). Dose-response in IgG antibodies ($p<0.001$). Haemorrhagic lung foci in highest exposure after PA dust challenge.	(165)
Rabbit	Subcutaneous	PA-RSA 0.25 ml weekly/12 weeks	High titre IgG to PA-RSA and PA-HSA, cross-reactivity with HHPA-, MHHPA- and MTHPA-HSA conjugates.	(66)
Mouse	Cutaneous	PA 4:1 in acetone:olive oil 50 μl on both flanks and after 7 days 1:1 dilution 25 μl x 2 on both ears	Marked total IgE elevation maximal after 14 days. IgE antihapten antibodies in PCA test. IgG_{2b} antihapten antibody production.	(32)
TMA				
Guinea pig	Intravenous immunisation, inhalation challenge	After 21-28 days tracheal challenge with 50 μl of 1% TMA-GPSA	Specific IgG_1 and IgE antibodies, increased lung resistance and airway microvascular leakage.	(70)
Rat	Inhalation	30-300 $\mu g/m^3$ TMA dust 6 h/day for 5 or 10 days	Haemorrhagic lung foci and TM-MSA antibodies after 10 days.	(211)
Rat	Inhalation	10 $\mu g/m^3$ TMA dust 6 h/day for 5 or 10 days	No effect on lungs.	(211)

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Table 8. Cont.

Anhydride/ Species	Route of administration	Exposure data	Effect	Reference
TMA				
Rat	Inhalation	500 μg/m^3 TMA powder 6 h/day on days 1, 5 and 10. On day 29 challenged 6 h to 540 μg/m^3	IgG-, IgM- and IgA-TMA-RSA antibodies, haemorrhagic foci mean 216/lung.	(208)
Rat	Inhalation	500 μg/m^3 TMA powder 6 h/day on days 1 and 5. On day 29 challenged 6 h to 500 μg/m^3	Haemorrhagic foci mean 112/lung, good correlation with antibody activity (p=0.027).	(208)
Rat	Intravenous immunisation, inhalation challenge	After 3 weeks challenged with 0.003 or 0.03% TMA-RSA (15 min) in 1 or 7 days	High levels of specific IgE and IgG (p<0.001), significant rise in bronchial hyperreactivity after repeated challenges (p<0.05), more often in low-dose challenge (p<0.05). Slight damage in airway epithelium in repeat-challenged groups.	(28)
Mouse	Inhalation	5 000 μg/m^3 TMA dust 1 h/day for 3 days	IgG-TMA-BSA antibodies after 1 week, IgE-TMA-BSA antibodies after 2 weeks.	(30)
HHPA and MTHPA				
Guinea pig	Intravenous immunisation, inhalation challenge	After 4 weeks HHPA- or MTHPA-GPSA 3 ml (nebulizer) or 0.01-1 000 μg/kg (iv)	Decrease in static compliance and arterial oxygen level and increase in inspiratory resistance after 10 minutes. Critical dose 40 μg/kg.	(221)

Table 9. Acute lethality data for organic acid anhydrides.

Anhydride	Species	Route of administration	LD$_{50}$ (mg/kg bw)	Reference
PA	Cat	Oral	800	(139)
	Rat	Oral	1 530	(139)
	Mouse	Oral	1 500	(139)
	Mouse	Intraperitoneal	75.5	(41)
TMA	Mouse	Oral	1 900	(15)
	Rabbit	Oral	5 600	(139)
MA	Rat	Intraperitoneal	97	(139)
	Rat	Oral	400	(139)
	Guinea pig	Oral	390	(139)
	Mouse	Oral	465	(139)
	Rabbit	Oral	875	(139)
	Rabbit	Dermal	2 620	(187)
MTHPA	Rat	Oral	2 140	(173)
THPA	Rat	Oral	5 410	(167)
TCPA	Rat	Oral	>15 800	(167)
	Rabbit	Dermal	>5 000	(167)

10.2 Effects of single and short-term exposure

Table 9 presents compiled data on the lethal dose for 50% of the exposed animals at single administration (LD$_{50}$) of organic acid anhydrides. PA and MA have the lowest LD$_{50}$-values in animal studies. In rats the oral LD$_{50}$ values are 400 and 1 530 mg/kg, respectively. TCPA is the least acutely toxic anhydride with LD$_{50}$ value >15 800 mg/kg orally in rats.

Oral TCPA (7 days, at 25 000, 100 000, 250 000 or 500 000 μg/kg in corn oil) has been shown to be a weak wide-spectrum inducer of microsomal enzymes in rats. A similar effect was not observed for mice (159).

10.3 Effects of long-term exposure and carcinogenicity

When rats, hamsters and monkeys were exposed to MA vapours (1 100-9 800 μg/m^3) for 6 months, no exposure-related effects were found in histopathological investigations of lungs, liver, spleen, bone marrow or kidneys. A histopathological examination of nasal tissue revealed irritation (hyperplasia, metaplasia) in rodent species and inflammatory changes in all species. All changes were judged to be reversible. In the metaplastic changes the cuboidal to low columnar epithelium became hyperplastic and pseudostratified. Transformation to nonkeratinising squamous-type epithelium was seen. Metaplastic changes were present at all dose levels with a nonlinear increase in incidence (171).

When rats were exposed to HHPA vapours at 34 300, 68 600 or 137 300 μg/m^3 (6 hours/day, 5 days/week for 2-11 weeks), their cerebral and cerebellar acetyl-cholinesterase activity was below the control range at 137 300 μg/m^3 after 2

weeks (p<0.01). After 11 weeks the activities had normalised to control levels. The creatine kinase activity increased in the cerebellar tissue after 11 weeks of exposure (p<0.01) (166).

Information on carcinogenicity of acid anhydrides is scarce. No evidence of carcinogenicity was found for PA in long-term feeding studies with rodents (65, 103, 104, 169).

When 6 rats where injected subcutaneously twice weekly with 2 000 μg of SA in 0.5 ml of arachis oil for 65 weeks, subcutaneous sarcomas developed at the injection site in the 3 rats that had survived 93-106 weeks. No tumours occurred in the 24 controls injected with arachis oil alone. The controls survived 45-106 weeks (77).

10.4 Mutagenicity and genotoxicity

No mutagenic activity has been found with PA, TCPA, or TBPA in *Salmonella typhimurium* in Ames test (121, 207). No effect of PA or TCPA was found on chromosomal aberrations neither in cells derived from Chinese hamster ovary cells nor in rat liver cells *in vitro* (49, 152).

Furthermore, when Chinese hamster ovary cells were tested for the induction of sister chromatid exchanges, PA and TCPA produced negative results (49). In a later chromosome aberration study using a higher and cytotoxic PA concentration (10 mM), an 18.5% increase in aberrations was seen compared to 3% in the control test (75).

There are no data on the mutagenicity or genotoxicity of other cyclic anhydrides.

10.5 Reproductive and developmental studies

Fabro *et al*. studied the teratogenicity of PA and SA in mice with daily intraperitoneal injections at doses of 0.2 to 0.6 mmol/kg/day on gestation days 8-10. They found malformations only at exposure levels of maternal toxicity (41).

No effects on reproduction were observed in CD-l mice when TMA (550 000 μg/kg) was given orally on days 7 through 14 of gestation (72).

No treatment-related effects on foetal development were seen in rats treated orally with MA in corn oil at a dose of 140 000 μg/kg/day from days 6-15 of gestation. Furthermore, no treatment-related effects on reproduction were observed with MA at doses up to 55 000 μg/kg/day over 2 generations (170).

PA caused malformations at a high frequency when 200, 100, 50, or 25 μg of PA per egg was injected into the air chamber of the egg of 3-day chicken embryos. A dose-response effect was found for early (105).

In conclusion, there is no evidence of teratogenic effects. However, only a few cyclic anhydrides have been tested.

11. Observations in man

Observations on human exposure are based on case reports of occupational sensitisations, industrial surveys, and some experimental human studies. In early reports the information on exposure levels is limited.

In humans, cyclic anhydrides cause irritation and sensitisation after direct contact with the skin and the mucous membranes or after exposure by inhalation (215).

The irritative symptoms (itching, lacrimation, sneezing, rhinorrhoea, cough, and dyspnoea) begin immediately at exposure to high concentrations of dust 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. A less frequent consequence is the severe disease called pulmonary disease-anaemia syndrome, and contact eczema, contact urticaria, allergic laryngitis, and allergic alveolitis. One case of haemolytic anaemia in an MA-exposed worker has also been reported.

11.1. Irritation and sensitisation

Conjunctival, nasal, and bronchial irritation is a common immediate feature following exposure to acid anhydrides (11, 126, 135, 136, 214). On mucous membranes and on sweating skin, they are hydrated to acids and can cause irritation, reddening, corneal damage, caustic dermatitis, and burns (122, 126).

The human nasal irritation threshold for PA has been reported to be 30 000 μg/m^3 and that for MA is 5 480 μg/m^3. However, exposure duration, generation of particles and particle sizes were not given (162).

Nielsen *et al*. studied 60 workers exposed to mean levels of 400 μg/m^3 PA with peak levels of 6 600 μg/m^3 during the loading of reactors. Of the 35 heavily exposed workers, 5 (14%) had asthma and 24 (69%) reported work-related symptoms of rhinitis and/or conjunctivitis. All the asthmatics were loaders. Four subjects had positive specific IgE, and 1 of the 4 suffered from asthma (136). The results indicate an irritative, non-allergic effect of PA on the mucous membrane. In a follow-up study, no significant effect on large airways, small airways, or alveolae was observed in the group of loaders when they were compared with the unexposed controls (130). When 20 HHPA-exposed subjects with work-related nasal symptoms were investigated, only 11 HHPA sensitised persons had positive reactions in the specific nasal challenge tests. The challenge test was negative in 9 subjects, all of them without HHPA sensitisation according to skin prick tests and determination of HHPA specific IgE antibodies but who nonetheless had irritant symptoms upon HHPA exposure (135).

Irritant haemorrhagic rhinitis has been reported as a result of MA exposure (18).

There is one report of anhydride-induced reactive airways dysfunction syndrome (RADS). RADS is characterised by damage of the bronchial epithelia followed by neurogenic inflammation and asthma (51). The person experienced acute mucosal symptoms immediately after an accidental 10-minute exposure to a

high concentration of PA. Symptoms of asthma developed, and 2 months later a nonspecific bronchial hyperreactivity was verified, which resolved after about 3.5 years (45).

11.2 Effects of repeated exposure on organ systems

Allergic reactions of the skin and conjunctiva and allergic respiratory manifestations are well known effects of occupational exposure to cyclic 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.

In industrial surveys the prevalence of occupational asthma due to different anhydrides has varied between 8-18% in those exposed to PA, 2-11% for TMA exposure, 15% for HHPA exposure, 11% for MHHPA exposure and 3-39% for TCPA exposure (203). According to the Finnish Register of Occupational Diseases, cyclic acid anhydrides caused the following numbers of diseases relative to the total numbers in 1997-1999: asthma 1/902, rhinitis 14/1 001 and contact urticaria 8/478. There were no reports of allergic alveolitis or allergic contact dermatitis (97-99).

There are no data showing an effect on other organ systems.

11.2.1 Allergic dermatitis
DSA sensitised a laboratory technician who prepared tissues for electron microscopy. The delayed-type allergic reaction was verified with positive patch tests with 0.5-1% DSA in acetone. Tests on 15 controls were negative. The patient did not react to epoxy resin, accelerator or another hardener (57).

A worker who used a horizontal boring machine contracted allergic contact dermatitis when exposed to MHHPA. Patch testing with a dilution series of MHHPA in petrolatum gave the following positive results: 2%, 1% and 0.5% ++; 0.25% and 0.125% +. 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 due to exposure to MHHPA, verified with positive skin prick tests and presence of specific IgE antibodies, and also erythematous skin symptoms in a chamber provocation test with MHHPA (96).

In a cross-sectional dermatological examination, 190 workers at 5 ceramics factories were investigated. The patch test series included MA (1% in ether) and PA (1% in petrolatum). Two workers had a positive patch test reaction to MA; no other data were available on these cases. The authors reported that, earlier, MA had been involved in 3 cases of skin sensitisation (129).

In 1955 urticarial reactions were reported among workers in PA production by Menschick (126) and Baader (11). There are, however, only a few case reports of immediate-type dermatitis due to acid anhydrides. MHHPA induced contact

urticaria in a worker from a factory where electronic components were filled with MHHPA-cured epoxy resin. The sensitisation was confirmed with the open test, which gave a positive reaction with the filling mixture and the hardener tested separately. Open tests with all the other components were negative, as were the epicutaneous tests with all the components. Open tests with the hardener were negative for 12 control persons (83). Tarvainen reported 2 cases of contact urticaria, one due to MHHPA, and the other due to MTHPA. Neither person had had skin contact with the anhydride; instead the exposure had only been airborne. Symptoms of urticaria began after 2 months of exposure. Later, conjunctivitis, rhinitis, and asthma symptoms also developed. An IgE-mediated allergy was diagnosed by means of skin prick tests and specific IgE antibodies (174). Another case of airborne contact urticaria due to MHHPA and HHPA has been reported for a winder in the electronics industry (95). CA has caused contact urticaria in a welder exposed to welding fumes of chlorinated polyester paint containing CA. An IgE-mediated allergy was verified with skin prick tests and specific IgE antibodies, and an open test with CA was also positive (102). MA has caused contact urticaria in an operator exposed to MA dust in a firm manufacturing polyester resin (94).

In conclusion, allergic dermatitis due to cyclic acid anhydrides is rare. There are only two case reports on delayed-type contact allergy, due to DSA and MHHPA. IgE mediated contact urticaria is more common, induced by contact or sometimes even airborne exposure to MA, MHHPA, MTHPA, HHPA and CA.

11.2.2. Respiratory allergies

Kern reported the first case of occupational asthma caused by an organic acid anhydride as early as 1939 (100). During the last 10 years a growing number of cases of asthma or rhinoconjunctivitis due to different acid cyclic anhydrides has been reported. The symptoms have been those of typical occupational asthma and rhinitis. After a symptom-free latency period the worker experiences symptoms when exposed to acid anhydrides at the workplace. The diagnosis has been based on the exposure, symptoms, and a cause-effect relationship proved with immuno-logical tests or challenge tests. In industrial surveys the diagnosis has often been based on questionnaire and immunological studies.

Reports of occupational asthma are presented in Table 10 according to the exposure. The more rare sensitising anhydrides are PMDA (epoxy glue (125), production of PMDA (18)), HA (manufacture of synthetic flame-retardants, (160)) and CA (in fumes of polyester paints, (102)). There are no reports of THPA- or TBPA-induced cases of occupational allergy.

Data from the industrial surveys on the findings of antibody formation and symptoms are compiled in Table 11.

Table 10. Type of industry or occupation in reports of occupational rhinitis and asthma.

Acid anhydride	Exposure situation/occupation	Reference
PA	PA production	(128)
	Production of alkyd or unsaturated polyester resins	(13, 136, 196)
	Paint factory	(43, 100)
	Varnish production	(54)
	Plastic grinder	(188)
	Chemical foreman	(120)
	Tyre and rubber manufacture	(27)
	Meat wrapper/price label fume	(110)
TMA	TMA production	(216)
	Mixing of TMA powder to epoxy resin	(164)
	Epoxy powder painting	(43, 109)
	Manufacture of cushioned flooring	(13)
MA	Epoxy resin insulation	(64, 171)
	MA production	(50)
	Alkyd or polyester resin production	(13, 108)
HHPA	Epoxy resin moulding	(127)
	Isolating of components for the electronics industry	(195)
	Production of electrical capacitors	(195)
	Production of epoxy hardener	(26)
MHHPA	Filling of electric components	(163)
MTHPA	Epoxy resin coating	(133, 137, 199)
TCPA	Epoxy resin production	(168)
	Epoxy resin coating	(76)

Table 11. Effects of cyclic acid anhydrides in occupationally exposed.

Anhydride/ Exposure level ($\mu g/m^3$)	No of exposed	Exposure duration m=months, yr=years	Symptoms, effects	Specific IgE	Specific IgG	Skin prick tests	Reference
PA							
<300-13 000 (TWA)	118	2 m-40 yr	Rhinitis 28 (24%) Asthma 21 (18%)				(196)
6 600 (1 500-1 7400) (TWA)	35	0-43 yr	Conjunctivitis 16 (46%) Rhinitis 14 (40%) Rhinoconjunctivitis 6 (17%) Asthma 5 (14%)	0.9 (0.5-28)	2.5 (0.7-7.1)		(136)
<100 (TWA)	25	0.3-40 yr	Conjunctivitis 5 (20%) Rhinitis 5 (20%) Rhinoconjunctivitis 3 (12%) Asthma 0 (0%)	1.5 (0.4-2.7)	1.5 (0.6-3.1)		
0	22		No symptoms	1.0 (0.4-2.2)	1.1 (0.5-3.2)		
TMA							
1 700-3 600 (TWA)	9	m-10 yr	Irritation 4/9 Asthma 3/9	1/9	4/9		(109)
10-2 100	18	8.6 yr	Rhinitis 1/18 Asthma 3/18	1/18, total TMA-HSA antibodies 4/18			(20)

Table 11. Cont.

Anhydride/ Exposure level (μg/m³)	No of exposed	Exposure duration m=months, yr=years	Symptoms, effects	Specific IgE	Specific IgG	Skin prick tests	Reference
TMA							
<1-100	11	2 yr	No symptoms	No antibody response			(124)
		Not given					(213)
170 (GM)	8		Asthma/rhinitis 2/8	25%			
87	39			0%			
<0.55	98		Asthma 1/98	0%			
<0.41	123			0%			
<0.53	42			0%			
full-shift		>1 m				TMA-HSA:	(13)
<10	63					1/63 (OR 1.00)	
10-40	36					5/36 (OR 10.00)	
>40	8					2/8 (OR 20.67)	
full-shift		>1 m	Risk of new work-related respiratory symptoms:				(13)
<10	44		5/44 (OR 1.00)				
10-40	13		6/13 (OR 5.94)				
>40	3		1/2 (OR 7.42)				

Table 11. Cont.

Anhydride/ Exposure level ($\mu g/m^3$)	No of exposed	Exposure duration m=months, yr=years	Symptoms, effects	Specific IgE	Specific IgG	Skin prick tests	Reference
HHPA							
3 800 (1 300-8 200)	11	Not given	Asthma 1/11 Rhinitis/conjunctivitis 9/11	4/11 (36%)	7/11 (64%)		(127)
1 900 (600-3 100)	16		Asthma 3/16 Rhinitis/conjunctivitis 13/16	7/16 (43%)	4/16 (25%)		
(HHPA and MHHPA)							(195)
0	26	5 yr		0%			
<10	37	6 yr		19%			
<10 (peak exposures)	19	10 yr		26%			
<10 (no peak exposures)	15	2.5 yr		0%			
10-<50	32	3.5 yr		34%			
≥50	26	5.5 yr		19%			
(HHPA and MHHPA) 38.7 (1-189)	37	33 (1-85) m		27%		21.6%	(193)
(HHPA and MTHPA) not measured	110	9.1 (6.8-36) yr	Work-related respiratory symptoms 14/110	17/110 (15.4%)			(35, 36)
after improvements <0.5-36	6	<4 yr		0/6			

Table 11. Cont.

Anhydride/ Exposure level (µg/m³)	No of exposed	Exposure duration m=months, yr=years	Symptoms, effects Eyes/upper airway	Asthma	Specific IgE	Specific IgG	Skin prick tests	Reference
MTHPA								
20-150	55	2.0 (0-6.0) yr	65%	11%	22%	24%		(134, 192)
5-20	70		56%	9%	16%	4%		
variable	19		42%	21%	16%	5%		
formerly 20-150, unexposed 1-5 yr	26	0.9 (0.2-2) yr	69%	8%	8%	0%		
unexposed referents	33		9%	0%	0%	0%		
10.1 (9-38)	81	26 (2-38) m			8.6%		4.9%	(193)
5.9 (0-50)	45	40 (1-105) m			8.9%		2.2%	
Plant A 25.5- 63.9 (GM)	37	5.6 (0.2-13) yr	More symptoms of eyes, nose and pharynx in plant A (p<0.02). No asthma in either plant.		64.9%			(202)
Plant B 4.93- 5.49 (GM)	58	12.4 (1.3-20) yr	More eye and nose symptoms in IgE-sensitised workers (p<0.05).		65.5%			
TCPA								
1. Moulders, constant exposure 210-390 (GM)	7	2.5 (0.1-8.1) yr	Work-related asthma 35%, mainly in moulding (work-related wheezing 27%, shortness of breath 29%, chest tightness 39%).		43%	57%		(118)
2. Intermittent exposure	6				67%	67%		
3. Coil assemblers	33				25%	34%		
4. Office workers	6				0%	0%		

GM: geometric mean.

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Determinations of specific antibodies

The proof of IgE mediation in immediate-type asthma or rhinitis due to acid anhydrides is convincing. When Kern reported the first case of asthma and rhinitis due to PA in 1939, he already had evidence of the immunological background. The scratch test with PA in crystalline form and diluted 1:1 000 in alcohol gave positive reactions. The tests with control patients were negative. The passive transfer test was also positive (100). Maccia and his colleagues were the first to find specific IgE in the serum of a patient with asthma due to PA in 1976. The patient experienced an immediate asthmatic reaction in the provocation test with PA dust (120).

Specific IgE has been found to PA, TMA, MA, TCPA, HHPA, HA, MHHPA, MTHPA, and CA (36, 76, 118, 120, 127, 134, 136, 160, 164, 176, 192, 193, 195, 201, 216). The induction time for positive specific IgE antibodies has been 8.8 (range 1-35) months when HHPA-, MHHPA-, and MTHPA-exposed workers were followed. The incidence of sensitisation was 4.1 cases/1 000 months at risk (193). The half time for specific IgE antibodies after cessation of the exposure was 1 year for TCPA and 0.9 year for MTHPA (186, 191). Commercial tests are available for measuring specific IgE antibodies for some anhydrides (123).

Inhibition studies and passive transfer studies have supported the specificity of IgE antibodies. However, cross-reactivity between some acid anhydrides has been reported (36, 119, 176, 190).

Immediate-type skin tests with acid anhydride-HSA conjugate have correlated well with the finding of specific IgE (17, 76, 143, 190, 192, 193, 216).

The location and specificity of the IgE antibody for the epitopes present on the acid anhydride (hapten)protein complex have been studied. It has been postulated that the reaction of acid anhydride with albumin alters the albumin to form a new antigenic determinant or that the hapten is altered at the antibody-combining site (19, 143, 210, 216). The formation of new antigenic determinants on the albumin site explains the cross-reactivity in the radioallergosorbent tests (RAST). There is evidence that in patients sensitised to TCPA and TMA, the antibody combines with the anhydride and the adjacent portion of the HSA molecule, whereas in patients sensitised to PA, the antibody is specific to the hapten (176). TMA is claimed to form unique antigenic determinants that do not bind significantly with antibodies formed by sensitisation to PA, HHPA and HA. This may explain why significant cross-reactivity with TMA has not been found in inhibition studies (19, 176, 216).

The workers exposed to either MTHPA or both HHPA and MHHPA have showed a marked cross-reactivity in skin prick tests, in the specific IgE determinations as well as in inhibition studies to MTHPA-HSA, HHPA-HSA, and MHHPA-HSA but not to PA-HSA and MA-HSA. For PA-exposed subjects the cross reactivity with other anhydrides was less pronounced (190).

The serum levels of specific IgE antibodies and interleukin-4 and interleukin-13 as Th_2 lymphocyte markers and interferon-gamma as a Th_1 lymphocyte marker were measured in 147 MTHPA-exposed workers. Work-related eye and nasal symptoms due to MTHPA were associated to the levels of interleukin-4 and also

interleukin-13. A shift in the balance between Th_1 and Th_2 cells was suspected due to the IgE mediated allergic response (204).

Specific IgG antibodies have been studied especially in connection with sensitisation to TMA. Specific IgG antibodies against TMA-HSA have been correlated with late-onset occupational asthma due to TMA. They have also been found in the pulmonary disease-anaemia syndrome due to TMA, as have IgG antibodies to erythrocyte conjugate (142, 144, 145, 164, 177).

Specific PA-IgG antibodies have been found in a worker exposed to PVC degradation products and phthalic acid esters. This finding indicates exposure to phthalic anhydride (131).

No cross-reactivity with PA, MA, HHPA, or TCPA was found when the specificity of IgG antibodies against TMA-HSA conjugate was investigated. In an equal test TMA-HSA was able to inhibit IgG bound to both PA-HSA and MA-HSA. Another antibody was suspected (53).

Nielsen and his co-workers have studied IgE, IgG, IgG_4, and IgM antibodies specific for PA in workers from alkyd or unsaturated polyester resin production. The mean level of exposure was 6 600 (1 500-17 400) μg/m^3 (time-weighted average, TWA) during loading and for full workday 400 μg/m^3. Of the heavily exposed workers, 69% had rhinitis and/or conjunctivitis and 5 workers (14%) had PA-induced asthma. There was a significant (p=0.01) difference between the heavy and low exposure groups only for specific IgG against PA. Only 1 worker with asthma had an increased specific IgE level. The subjects with asthma had significantly higher values for specific IgG than the asymptomatic subjects. Specific IgG_4 was found in 4 persons, 3 had asthma and 1 had rhinitis. The authors concluded that specific IgG is an index of PA exposure, and that specific IgG_4 may be a pathogenetic factor in asthma (136).

In TMA-exposed workers, the levels of IgG_{1-4} subclasses against TMA-HSA did not differ between workers with and without a TMA-induced immunological lung disease (52).

In MTHPA-exposed workers no association between work-related symptoms and specific IgG_4 antibodies was found, but the intensity of the exposure was the major determinant of specific IgG_4 levels (201, 205).

Reports of allergic occupational diseases due to cyclic anhydrides: PA
Wernfors *et al*. studied 118 workers in four plants producing alkyd or unsatu-rated polyester resins. Forty-eight were current employees and 70 were former employees. The PA dust concentrations during the loading of the reactors and in the handling of bags were very high, up to 13 000 μg/m^3. The fraction of respirable dust was about 40%. The authors found 28 (24%) persons with work-related rhinitis and 21 (18%) with asthma. Eleven per cent had symptoms of chronic bronchitis. In 10 of the 21 asthmatics, rhinitis preceded the asthmatic symptoms. The latency period before the onset of the respiratory symptoms ranged from 1 month-16 year. A positive skin-scratch test was found in 3 of the 11 asthmatics but in none of the non-asthmatics. A Prauznitz -Küstner test was

positive with serum of 2 asthmatics. The same patients were challenge tested. The bronchial provocation tests with PA powder 6 000 μg/m^3 (5 minutes) caused a dual asthmatic reaction in the first patient, whereas the test with 500 μg/m^3 was negative. The second patient experienced a dual reaction when challenged with the lower PA concentration (196).

When the exposure level of PA was measured (Table 11), the full day TWA for PA was approximately 400 μg/m^3, well below the Swedish exposure limit value 6 000 μg/m^3 at that time. The authors then suggested a ceiling value below 6 000 μg/m^3 for PA (136).

Reports of allergic occupational diseases due to cyclic anhydrides: TMA
Both immediate- and late-type respiratory allergies have been reported due to TMA. Both begin after a latency period. Specific IgE antibodies have been found in immediate-type rhinitis and asthma (144, 214). In the late-type respiratory syndrome the worker experiences coughing, wheezing and dyspnoea, starting 4-8 hours after the exposure. The respiratory symptoms have been accompanied by malaise, chills, fever, myalgia and arthralgia. No specific IgE antibodies are found, but IgG and IgA antibodies are present (144, 214). The disease has not been verified with challenge tests. An irritant reaction has been postulated (183).

Pulmonary disease-anaemia syndrome due to TMA is a disease first reported by Rice *et al.* in 1977. Herbert and Orford reported 7 more cases in 1979, and Ahmad *et al.* presented another 2 in 1979. All cases had been exposed to fumes from TMA-cured epoxy resin sprayed on hot pipes. The symptoms were cough, haemoptysis, dyspnoea, pulmonary infiltrates, restrictive respiratory defect, hypoxaemia, and anaemia. The symptoms ranged from mild to very severe. A possible fatal case was identified (2, 74, 142, 157). IgG antibodies have been found to both human serum conjugate and erythrocyte conjugate of TMA. Open lung biopsy has shown intact alveolar septae and extensive intra-alveolar haemorrhage with granular pneumocyte hyperplasia. Immunofluorescent studies were negative, suggesting that the antibodies were not involved in the tissue injury (2, 74, 144, 157, 214). Patterson *et al.* did not find any IgE antibody activity against trimellityl-HSA (TM-HSA) in workers with pulmonary disease-anaemia syndrome. IgG activity against TM-HSA did not differ from the level in other workers exposed to TMA fumes under similar work conditions. IgG, IgA and IgM antibodies were found against TMA-human erythrocytes (142). Later, antibodies to TMA-human erythrocytes were also found in workers with asthma due to TMA, but not in unexposed persons (177).

All 9 workers from a barrel manufacturing plant were investigated because of their exposure to TMA. The levels of TMA in the personal breathing zone were 1 700-3 600 μg/m^3. One worker was asymptomatic. Four workers had TMA-induced irritant effects. Three had symptoms and IgG levels consistent with late-type respiratory syndrome. One of them also had specific IgE against TMA. One worker had bronchitis not related to TMA (109).

In a factory preparing epoxy resin coating material the exposure level for TMA was less than 180 μg/m^3 after improvements in work hygiene. During two years no TMA related diseases were found among 11 workers (124).

In the TMA manufacturing industry, a 12-year (1976-1987) clinical and immunological evaluation of 196 workers was carried out. The diagnosis was based on results of a questionnaire, an interview and immunological studies for total TMA antibodies and TMA-specific IgE. IgE-mediated immediate-type asthma or rhinitis was found in 21 workers and late-type asthma in 10 workers, and yet another worker had pulmonary disease-anaemia syndrome. A total of 113 workers had only irritant symptoms, and 46 were asymptomatic. A low level of total antibodies was found for TMA-HSA in 16% and 8%, respectively. No data were available on the exposure. There was, however, an annual decline in the number of sensitised workers due to improvements at the workplace (212).

In the same factory, in a cross-sectional study of 474 workers in 1988-1989 with a very similar setting, five exposure groups were assigned by an industrial hygienist on the basis of job history and the results of personal monitoring of some employees in each exposure class. Seven per cent had an immunological syndrome due to TMA exposure, and 32% had irritant symptoms with low specific total and IgE antibody levels. Sixty-two per cent had no work-related symptoms and very few or no antibodies. The mean total antibody levels and mean IgE antibody levels decreased according to the exposure level. TMA specific IgE antibodies were found only in the high exposure group (0.54-6 500 μg/m^3, geometric mean 170 μg/m^3) whereas the findings were negative in four other groups with exposure less than 6-970 μg/m^3 (geometric mean 87 μg/m^3) of TMA. The sensitisations and illnesses due to TMA were concentrated into the three upper exposure groups, and therefore efforts to reduce exposure were suggested. A group of new employees not evaluated earlier for an occupational disease were analysed for total TMA-HSA antibody levels by age, sex, date of hire and smoking. Only current or former smoking was associated with the total antibody levels (x^2=6.45, p=0.01). Atopic status was not assessed (213). One year after 29 sensitised workers had been moved to low-exposure jobs, their symptoms and pulmonary functions had improved and the specific antibody levels had decreased (60).

One case of allergic alveolitis has been reported in connection with exposure to both TMA and PA. The worker was exposed to the dust and fumes of polyester powder paint during a malfunction of the ventilation of the factory hall. The paint contained small amounts (<1%) of both TMA and PA. The diagnosis was based on the follow-up of the symptoms and on the findings in chest radiographs and BAL, as well as on the presence of fever and a slight reduction in the transfer factor after a short re-exposure at work (153).

Reports of allergic occupational diseases due to cyclic anhydrides: MA
Durham reported in 1987 the results of the MA challenge tests of 2 MA-exposed workers (a storeman and a batch weigher). In both cases control tests were negative and dual asthma reactions due to MA were verified (37). In another

report a worker developed cough, rhinitis, breathlessness and wheezing after one month of exposure to PA and MA. The dust exposure during the emptying of bags was 330 μg/m^3 for PA and 170 μg/m^3 for MA. The worker was a smoker. An atopic tendency was found in the skin prick tests, and he had nonspecific bronchial hyperreactivity. In the bronchial challenge tests with MA crystals he experienced a dual asthmatic reaction, whereas the test with PA was negative. The dust concentrations were well below those measured from the workplace. No skin prick tests or antibody determinations were carried out (108).

A worker in MA production who had previously had MA-related asthmatic symptoms developed severe haemolytic anaemia. He relapsed two weeks after the return to work the next year. Afterwards he remained stable as long as he avoided MA exposure. He had high titre of MA-specific IgE but not IgG antibodies. The Coombs test was positive but no antibodies to MA red-cell conjugate were found. There were no symptoms of pulmonary haemorrhage in conjunction with pulmonary disease-anaemia syndrome due to TMA exposure (50, 81).

Reports of allergic occupational diseases due to cyclic anhydrides: HHPA
In 1985 Moller reported the first cases of occupational sensitisation to HHPA from exposure to epoxy resin moulding. Twenty-seven workers were evaluated on the basis of the results of a questionnaire, pulmonary function tests, and antibody determinations. The concentration of HHPA was very high when compared to the more recent studies (Table 11). All 4 cases with symptoms of occupational asthma had specific IgE to HHPA conjugates, as did 6 of 22 cases with rhinitis and/or conjunctivitis. In the specificity studies both HHPA-HSA and PA-HSA were effective inhibitors (127).

Erosions of the nasal mucosa and epistaxis have been described in connection with IgE-positive occupational rhinitis due to HHPA. All the patients also had high titres of specific IgG. The HHPA concentration was not determined, but it was not considered high enough to cause tissue destruction (61). The same group followed 28 employees with HHPA-induced asthma or rhinitis for least one year after removal from exposure. The symptoms and spirometry normalised in all but 1 worker. There was a decline in the HHPA-specific IgE in 25 workers (59).

Chee *et al.* diagnosed a case of asthma due to HHPA in the manufacture of epoxy resins. The hardener consisted mainly of HHPA but also of an amine as an additive. In the process the hardener was heated to 130°C. The long-term follow-up of peak expiratory flow showed deterioration during the workweek and improvement during days off. The authors also carried out challenge tests. A control test where an empty tin was heated was negative. When 200 ml of pure HHPA was heated to 92°C, the patient experienced a severe immediate and also a late long-lasting asthmatic reaction. No skin prick tests or antibody determinations were carried out (26).

Nielsen *et al.* investigated the allergic aetiology of work-related nasal symptoms of HHPA-exposed workers. Nasal challenge tests with HHPA-HSA conjugate were carried out. The results were positive in 11 subjects sensitised to HHPA (positive skin prick tests and specific IgE antibodies) and negative in 9

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non-sensitised subjects, in spite of work related irritation symptoms in the non-sensitised individuals (135).

Reports of allergic occupational diseases due to cyclic anhydrides: MHHPA
MHHPA has caused sensitisation and respiratory symptoms (96). A rare case of specific MHHPA-induced laryngitis has been reported in an electrician. A skin prick test with MHHPA conjugate was positive, and specific IgE antibodies to the conjugate were found. The laryngeal reaction was verified by a challenge test with MHHPA (163).

Reports of allergic occupational diseases due to cyclic anhydrides: MTHPA
Nielsen *et al*. found a case of work-associated asthma and rhinitis in a subject exposed to MTHPA used as an epoxy-curing agent in the preparation of barrels for grenade firearms. MTHPA-HSA-specific IgE antibodies were found, but specific IgG antibodies were not present. A skin prick test was positive with the same conjugate but negative with PA-HSA (137). Later the work force of the factory was examined for symptoms, exposure, antibody response, lung functions and risk factors. In a group consisting of 140 currently and 26 formerly exposed workers, they found higher frequencies of work-related symptoms of the eyes (31 versus 0%), nose (53 versus 9%), pharynx (26 versus 6%) and asthma (11 versus 0%) than among 33 controls. The rate was 16 for positive skin prick tests with MTHPA-HSA conjugate, 18 for specific IgE antibodies and 12 for specific IgG antibodies, while for the controls all the tests were negative. There were statistically significant exposure-response relationships between the exposure and symptoms of the eyes and upper airways, dry cough, positive skin prick tests and specific IgE and IgG antibodies. The concentration of MTHPA was under 150 μg/m^3. The median exposure time for specific IgE positivity was 5 (range 0.2-5) years. A close association between specific IgG_4 and total specific IgG was found. Up to 91-95% inhibition of the IgE-MTHPA-HSA binding was reached with MTHPA. There were no significant differences in lung functions between sensitised and non-sensitised subjects. No association between sensitisation and either atopy or smoking was found. They found that significantly more former workers than current ones had positive skin prick tests with common allergens; atopic workers tended to withdraw from the exposure early, perhaps even before clear work-related symptoms appeared (133, 134, 192).

The decline in serum antibodies to MTHPA was followed in 10 workers after the cessation of exposure an average of 54 months earlier. The mean individual half-time for specific IgE was 0.9 years, and for specific IgG it was 0.4 years. In addition, 4 workers who moved to jobs with significantly reduced exposure were followed, and corresponding decreases in antibodies were seen. No correlation was found between the half-times of specific IgE and total IgE, atopy, smoking or gender (191).

Yokota *et al*. studied the workers at two plants where condensers for electric appliances were manufactured and MTHPA was used as a hardener in the epoxy resin insulation. Some workers had had work-related nasal symptoms. At first the

authors studied 28 workers exposed to MTHPA levels between 1.09 and 22.4 μg/m^3. Specific IgE antibodies were detected in 9 (32%) of the workers. Eight of them had nasal symptoms. The authors also found that the total IgE levels were significantly higher in the group with specific IgE, and suggested that total IgE can be used in the selection of workers (199).

A later study group consisted of 148 workers, of whom 66% had specific IgE antibodies. The authors further found that the relative risk for elevated MTHPA-specific IgE for smoking was 4.1. In the group with a high total IgE, the relative risk of producing IgE antibodies to MTHPA was 4.7 in a comparison with the group with a low total IgE (<80 IU/ml) (200).

In a study of the exposure-response relationship, the minimal level for an association between MTHPA exposure and work-related symptoms was 15-22 μg/m^3. It was suggested that exposure above 15 μg/m^3 should be avoided to prevent the development of occupational allergic diseases among most workers (202).

In 1991, Drexler *et al.* investigated 110 workers exposed to HHPA and MTHPA and found that 20 of them were sensitised according to skin prick tests and specific IgE determination. In challenge tests occupational asthma or rhinitis was verified for 6 cases. The concentrations of acid anhydrides in air were not measured. In the end of 1991 the hygienic conditions at the plant were improved. In 1995 a new study was carried out that also included people who had left the plant since 1991. The relative risk of people sensitised in 1991 leaving the plant between 1991 and 1995 was 2.6 compared with people without any sign of sensitisation. The rate of sensitisation was 21%. None of the 6 persons employed after 1991 showed evidence of sensitisation. Five of the 6 persons with verified sensitisation in 1991 were still at the workplace. All of them reported fewer symptoms than before. The exposure level was measured in 1995, and it was <0.5-36 μg/m^3 (35, 36).

Reports of allergic occupational diseases due to cyclic anhydrides: TCPA
In 1987 five cases of occupational asthma due to TCPA in epoxy resin were reported. The diagnoses were confirmed in 3 workers by dual asthmatic reactions in inhalation challenge tests. TCPA-bovine serum albumin conjugate was used to detect specific IgE antibodies. No antibodies were found (168).

TPCA has been used as an epoxy-resin curing agent since 1979 in an epoxy-coating process in a factory making electronic components in the United Kingdom. Seven cases of occupational asthma were diagnosed in 1979-1980. Inhalation challenge tests with controlled TPCA concentrations from 1.3-961.1 μg/m^3 with both immediate and late reactions confirmed the diagnoses. Specific skin prick tests were positive, and specific IgE antibodies against TCPA-HSA conjugate were detected. The factory was closed in 1980 (76, 184). A 12-year follow-up showed that symptoms at first improved, but then remained unchanged. All the cases still had daily or weekly symptoms. The bronchial hyperresponsive-ness had also persisted. Specific IgE antibodies fell slowly with a half-time of 1 year (12, 186).

In a Canadian cross-sectional study of 56 workers in a factory using TCPA-cured epoxy resin for about 2 years, the prevalence of work-related respiratory symptoms was high, 27-39%. According to a questionnaire, occupational asthma was present in 35% of the workers. Thirty-one per cent had specific IgE, and 39% had specific IgG against TCPA-HSA. The mean TCPA concentration was between 210-390 μg/m^3. The prevalence of specific IgE was highest among those who had the jobs with the highest exposure. After the ventilation was improved and exposure was reduced to less than 110 μg/m^3, the symptoms decreased, and no new cases of occupational asthma were found (118).

Reports of allergic occupational diseases due to cyclic anhydrides: PMDA
In 1980, Meadway reported 2 cases of asthma from exposure to PMDA-cured epoxy resin when glue was mixed, used and cured. The workers underwent challenge tests simulating work with the mixture, and the results were positive. Five other workers had negative test (125).

Next report on PMDA is from year 1995. A cross-sectional and follow-up study was carried out with 92 workers with exposure mainly to PDMA but also to PA, MA or TMA. Of those with less than one year of exposure, 56 workers had work-related symptoms. Eighteen had dyspnoea, and 8 had bronchial obstruction. Specific IgE antibodies were found only in 15 workers, of them 12 had symptoms. The authors also found 11 cases of haemorrhagic rhinitis that occurred after more than 15 years of exposure. Only one of the cases had specific IgE antibodies. After 10 months both the symptoms and the bronchial obstruction of the group no longer exposed had diminished, whereas the workers still exposed had comparable pathological findings in the re-examination. The symptoms were reversible in workers whose exposure stopped after a work period of about 0.7 years. No relevant specific IgG antibodies were detected in this group (18).

A case of acute haemorrhagic alveolitis associated with anaemia similar to pulmonary disease-anaemia syndrome due to TMA has been reported for PMDA exposure. PMDA in powder form was used as a cross-linking agent in epoxy resin production. High concentrations of PMDA-specific IgG antibodies were found and also TMA-specific IgG antibodies, but not PA- or MA-specific IgG antibodies. The patient had no specific IgE antibodies. The Coombs test was negative (29).

Reports of allergic occupational diseases due to cyclic anhydrides: HA
A worker exposed to HA powder in the manufacture of a synthetic flame retardant developed after one year rhinitis, hives, and wheezing at work. He and 2 of the 6 other symptomatic workers of all 20 tested had specific IgE antibodies for HA-HSA conjugate. In RAST inhibition studies HA-HSA showed the highest inhibition. A cross-reactivity was found with HHPA-HSA but not with PA and TMA conjugates (160).

Reports of allergic occupational diseases due to cyclic anhydrides: CA
A welder developed work-related urticaria and asthmatic symptoms when exposed to the thermal degradation fumes from a polyester paint. The paint contained both alkyd resins and chlorinated polyester resin. A new sensitising anhydride, CA, was identified from the hardener. A skin prick test with CA-HSA conjugate was positive, as was an open test for urticaria. CA-HSA-specific IgE antibodies were also detected. Significant decreases in peak expiratory flow measurements were seen after short (10 seconds) welding procedures (102).

Concluding remarks
The reports of occupational asthma and rhinitis due to PA are mainly dated to the years 1980-1990. The case reports and industrial surveys on TMA-induced work-related respiratory symptoms are likewise not very recent. During last decade MTHPA and HHPA have been the main topics of concern. The exposure levels have decreased with improved work hygienic control, but exposure peaks still occur.

The respiratory allergies have mainly been IgE mediated. Specific IgE antibody determinations and skin prick tests are relevant methods when investigating the aetiology of work-related symptoms. Specific IgE antibodies cannot, however, be used to assess exposure at the work place. The half-time of specific IgE antibodies after cessation of the exposure has been about 1 year.

The 12-year follow-up study of TCPA-induced asthma showed a poor prognosis for occupational asthma despite cessation of the exposure. Equally long follow-up studies are not available on occupational asthma induced by other cyclic acid anhydrides.

11.2.3 Predisposing factors for cyclic acid anhydride-related allergy
Venables and co-workers studied the effect of smoking and atopy on antibody E production in 300 TCPA-exposed workers. Atopy was defined as at least one positive skin prick test to common allergens. Twenty-four of the workers had specific IgE to TCPA. Twenty of them (83.3%) were current smokers compared with 133 (48.2%) of 276 without antibodies (p<0.01). Atopy was also more common in those with specific IgE, but not significantly so. Smoking and atopy interacted, the prevalence of antibody being 16.1% for atopic smokers, 11.7% for nonatopic smokers, and 8.3% for atopic non-smokers (p>0.025). The authors concluded that smoking may interact with atopy in the production of specific-IgE antibodies to TCPA (185).

In a study of 55 workers highly exposed to MTHPA no significant differences were found between the subgroups for atopy and smoking habits according to IgE sensitisation. In the same study with a total of 144 exposed workers the group of former workers had positive skin prick tests to common allergens significantly more often than unexposed controls. The authors suggested that atopic workers tend to withdraw from exposure early because their mucous membranes are more reactive and therefore atopic persons do not seem to run a particular risk of sensitisation to small reactive organic molecules (134).

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In a recent prospective study, 163 workers exposed to HHPA, MHHPA and MTHPA were followed for 32 (1-105) months. The mean combined exposure level was 15 (range <1-189) μg/m^3. Thirteen per cent of the workers had positive specific IgE. An association was found between exposure and atopy, respectively, and the induction of specific antibodies. The odds ratio for atopics to get IgE sensitised as compared with non-atopics was 6.0 (95%CI 2.2-16.6). Subjects with a mean exposure of >15 μg/m^3 had a significantly higher risk for development of specific IgE (odds ratio 3.4; 95%CI 1.2-9.4) than subjects with a mean exposure of <10 μg/m^3. The risk for atopics was comparable with the risk for the subjects in the most exposed group. The effect of smoking was not significant (193).

In a Canadian study of 148 MTHPA-exposed workers a correlation was found between total IgE and specific IgE (p<0.0001). Current smoking was significantly associated with specific IgE production only in the group with low total IgE, <100 kU/ml (200).

Altogether 119 TMA-exposed workers were followed for five years to determine whether they would develop a respiratory disease. Sixteen had TMA-specific IgE antibodies and 3 of them had asthma in the beginning. Another 6 developed asthma during the 5-year follow-up period. One of the 102 workers with no specific IgE antibodies developed asthma. Specific IgG antibodies were detected in 44 subjects, 6 had a non-immediate respiratory disease in the beginning and 2 more were found after five years. None of the IgG-negative workers developed a respiratory disease (58). In a study of 57 HHPA-exposed workers, 7 had IgE and IgG-mediated respiratory disease whereas 9 had only IgE-mediated disease. An association was found between the development of respiratory disease and specific IgE and IgG antibodies, as well as an association with the level of exposure but not with smoking (62). Skin prick test reactivity to common allergens in 33 employees with respiratory symptoms due to HHPA showed that atopy had only a marginal clinical significance as a risk factor for disease (63).

In a case-control study of 16 persons with TMA asthma and 44 similarly exposed controls, determinations of specific IgE against four common environmental allergens were carried out. Fifty-six per cent of the cases and only 29% of the controls were found to be atopic (172).

Risk factors for sensitisation and respiratory symptoms were evaluated in a historical cohort study consisting of 506 workers from four factories. The cohort was defined as all workers with exposure to anhydrides for more than one month since the beginning in 1960. Three factories manufacturing resins used principally PA, but also MA and TMA were used. One factory produced cushioned flooring and used only TMA. The exposure was assessed retrospectively, by job. The current full-shift and task-specific exposure measurements, the past exposure data and qualitative information were used and exposure estimates were calculated in the job-time-exposure matrices (181). The questionnaire, comprising employment history, respiratory symptoms and smoking habits, was completed by 401 workers (79%). Skin prick tests with common inhalant allergens and anhydride conjugates were carried out. Thirty-four persons (8.8%) had respiratory symptoms related to

anhydride exposure, and 12 (3.2%) were sensitised according to the skin prick tests with anhydride conjugates. Sensitisation was associated with work-related respiratory symptoms and with smoking, at the time of the exposure to acid anhydride. An exposure-response relationship was not found overall, but in the factory with exposure to TMA an increased prevalence of sensitisation and work-related symptoms with increasing full-shift exposure:<10, 10-40 μg/m^3 and >40 μg/m^3 of TMA was observed. The relation was apparent within the current occupational exposure standard of 40 μg/m^3 and it was not modified significantly by smoking or atopy. Exposure to PA or MA was found to be uncommon as a cause of sensitisation at the low exposure levels measured, 8.9-11.9 μg/m^3 and 1.8-2.8 μg/m^3, respectively (13).

The association of human leukocyte antigen (HLA) allele frequency and specific IgE antibody to acid anhydride-HSA conjugates has been investigated to determine a possible genetic influence on sensitisation. Thirty workers with work-related respiratory symptoms with specific IgE antibodies had been exposed to PA, TMA, or TCPA. Thirty referents were exposed to PA or TMA. A similar proportion of both the cases and referents were atopic and smokers, the other risk factors for this sensitisation. A significant excess of HLA-DR3 loci were found in cases with specific IgE to acid anhydrides when compared with the controls (50% versus 14%). A relationship was found between HLA-DR3 and specific IgE antibodies for TMA and possibly for TCPA but not for PA. The difference in the epitope was suggested as the reason for the different findings (206).

Altogether 57 HLA antigens were analysed in MTHPA- or HHPA-exposed workers. Fifty-three were sensitised according to the specific IgE antibodies and positive skin prick test. Forty-seven non-sensitised exposed workers were controls, as was a group of unexposed subjects. Only for HLA-A25 and HLA-A32 statistically significant differences were found between the sensitised and non-sensitised workers, 0% versus 9% and 0% versus 13%, respectively. An HLA-antigen-associated immune protective factor was suspected to reduce the risk of sensitisation. An association HLA-DR3 was not found for MTHPA-sensitised workers, as in an earlier study on TMA-sensitised workers (132).

Concluding remarks
In TCPA-exposed workers smoking and atopy have been found to interact in the production of specific-IgE antibody to TCPA. In a prospective study on HHPA-, MHHPA- and MTHPA-exposed workers, a significant effect of atopy, as well as of exposure, on sensitisation was observed. The influence of smoking on sensitisation was not significant.

The influence of smoking and atopy on TMA sensitisation has been non-significant. Increasing full-shift exposure to TMA has been a predisposing factor for sensitisation.

There are also two studies on the genetic background of sensitised persons. A relationship was found between HLA-DR3 and specific IgE antibodies for TMA and possibly for TCPA but not for PA. When MTHPA- and HHPA- exposed

workers were investigated no such association was found but an HLA-A25 and HLA-A32 associated immunoprotective factor was suspected.

11.3 Genotoxic effects

There are no data on genotoxic effects of cyclic acid anhydrides in humans.

11.4 Carcinogenic effects

In a case-control study mortality from lung cancer was investigated in a plant producing acetylene and PA. After control for age and smoking, the odds ratio for lung cancer mortality among the 43 subjects exposed in the factory was 5.6 (95%CI 1.9-16.2). The corresponding odds ratio for 99 referents from other work environments in the region was 1.7 (95%CI 0.9-3.5). There was, however, exposure also to phthalates and soot (156).

11.5. Reproductive and developmental effects

There are no data on the developmental effects of cyclic acid anhydrides on human reproduction.

12. Dose-effect and dose-response relationships

12.1. Single and short-term exposures

The acute effects of cyclic anhydrides on animals have generally been found to be irritation of mucous membranes after direct exposure (Table 7).

The human nasal irritation threshold for PA has been reported to be 30 000 μg/m^3 and that for MA to be 5 480 μg/m^3 (162). However, exposure type and duration, generation of anhydrides, and particle sizes were not given. In early reports, irritation of the mucous membranes was a common immediate response in workers highly exposed to acid anhydrides in powder form (11, 126, 136). In workers exposed to high levels of TMA, rhinorrhoea, cough, and dyspnoea have been reported already after the first exposure (214). In more recent studies irritant symptoms of eyes and upper airways have been detected after relatively low exposure (150 μg/m^3 TWA) of MTHPA (134).

Immunisation of animal species verified with specific IgE and IgG antibodies, followed after cutaneous administration or single intradermal injection with free or conjugated PA, TMA, MA, HHPA, MHHPA, MTHPA, THPA and SA (Table 7 and 8). Repeated short-term exposures (subcutaneous or inhalation) with PA or the corresponding conjugate induced specific IgG antibody formation in a dose-response manner in guinea pigs. In challenges after sensitisation, more positive tests were seen when a higher dose was used (165) (Table 8).

In inhalation challenge tests in rats, concentrations of 30-300 μg/m^3 of TMA dust induced haemorrhagic lung lesion and antibodies, whereas 10 μg/m^3 had no effects (211).

12.2 Long-term exposure

Long-term dose-response studies (animals) are few. Rats, hamsters and monkeys were exposed to 1 100-9 800 μg/m^3 concentrations of MA 6 hours/day 5 days/ week for 6 months. Nasal and ocular irritation and metaplasia of nasal mucosa were found at all the exposure levels only in rodents being obligate nose breathers (171).

Human data derived from industrial surveys have been compiled in Tables 10 and 11.

In a survey with a total exposure time of about 40 years, 46% in the high exposure group (1 500-17 400 μg/m^3 of PA) 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 PA exposure (136).

In a historical cohort study of PA- and MA-exposed workers sensitisation was found to be uncommon at the low exposure levels measured, 8.9-11.9 μg/m^3 and 1.8-2.8 μg/m^3, respectively (13).

When TCPA had been in use for two years, 35% of the 56 exposed workers had occupational asthma according to a questionnaire, and 31% had specific IgE antibodies. The exposure levels to TCPA in preforming and moulding had been between 140-590 μg/m^3. The next year, after the ventilation was improved, the TCPA exposure fell to 30 μg/m^3 in preforming and to <10-110 μg/m^3 in moulding. After that, work-related symptoms decreased and no new cases of occupational asthma have been reported (118).

In a historical cohort study of TMA-exposed workers, the prevalence of sensitisation and work-related symptoms increased with increasing exposure. In workers exposed to 10-40 μg/m^3 or >40 μg/m^3 of TMA compared to the workers exposed to <10 μg/m^3, the odds ratio for positivity was for TMA skin prick tests 10.0 and 20.7 and for the risk of new work-related respiratory symptoms 5.9 and 7.4, respectively (13).

In workers exposed to HHPA and MHHPA at levels of <10, 10-50 and >50 μg/m^3 specific IgE antibodies were found. There were no differences in levels of the specific IgE antibodies between the exposure groups. The workers in the low exposure group had, however, occasionally had higher exposure peaks (195). Among MTHPA-exposed workers, even at low levels of exposure (5-20 μg/m^3) 56% had symptoms of the eyes and upper airways, 9% had asthma, and 16% had MTHPA specific IgE antibodies. The corresponding numbers were 65%, 11%, and 22% in the more heavily (20-150 μg/m^3) exposed groups (134, 192).

When HHPA- and MHHPA-exposed workers were followed for a mean period of 33 months (range 1-85), 27% had been sensitised and had specific IgE

antibodies. Altogether 21.6% had positive reactions in skin prick tests with corresponding HSA-conjugates. The exposure level was 38.7 (range 1-187) μg/m^3. In workers exposed to MTHPA at levels 10.1 (range 9-38) and 5.9 (range 0-50) μg/m^3 the percentage of positivity for specific IgE antibodies were 8.6% and 8.9% and for skin prick tests 4.9% and 2.2%, respectively. The observation times were 26 (range 2-38) and 40 (range 1-105) months. There was no statistically significant difference between peak exposure levels in sensitised and nonsensitised workers in these studies (193).

Concluding remarks

Immunisation has been induced by a single intradermal dose of various cyclic anhydrides in animals. Exposure to high as well as low levels has without any latency period caused irritant symptoms in workers. Metaplasia of nasal mucosa has been seen in animals after long-term exposure to high levels of MA. The data on dose-response of sensitisation, and work-related symptoms are too limited for determining any lowest observable adverse effect level, but in industrial surveys TCPA and PA have induced sensitisation and asthma in workers exposed to the concentrations 140 and 1 500 μg/m^3, respectively. TMA, HHPA, MHHPA, and MTHPA have caused both sensitisation and work-related symptoms at exposure levels as low as 5-50 μg/m^3.

13. Previous evaluations by national and international bodies

The documentation of the American Conference of Governmental Industrial Hygienists (ACGIH) was revised for PA in 2000, for TMA in 1993 and for MA in 2000. PA was defined as an irritant and sensitiser of the skin and respiratory tract and potent ocular irritant. The potency of irritancy was considered lower than that of MA. TMA was defined as irritant to the respiratory tract, the eyes, and skin and also as sensitiser in repeated exposure. To prevent sensitisation, a ceiling value was recommended in 1993. MA was defined as an irritant of the skin, eyes and upper respiratory tract, and as a sensitiser of the respiratory tract. According to ACGIH, PA and MA are not classifiable as human carcinogens (1).

The Health and Safety Executive (HSE) in the United Kingdom published a document on three acid anhydrides in 1996 (PA, TMA, and MA). The principal adverse effects of exposure in humans were stated to be asthma and respiratory tract irritancy and, for TMA, also other respiratory effects, which may be accompanied by systemic toxicity. Asthma was regarded as a serious health effect, and therefore the assignment of maximum exposure limits was indicated for each substance. A special notation of the respiratory sensitisation properties of each substance was added (158).

SA has been evaluated by the International Agency for Research on Cancer (IARC); limited evidence of a carcinogenic effect was reported for animals, but SA was not classifiable as carcinogen in humans (group 3) (78).

Chlorendic acid, the hydrolysis product of CA, has been evaluated by IARC. The evidence was sufficient for the carcinogenicity of chlorendic acid in experimental animals. There are no data on its carcinogenicity in humans, but, overall, it was concluded that chlorendic acid is possibly carcinogenic to humans (Group 2B) (79). In the evaluation of the International Programme on Chemical Safety (IPCS), separate carcinogenicity studies with CA were not considered necessary, since the compound is metabolically transformed to chlorendic acid (80).

In the European Union commission directives on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances, PA, TMA, MA, HHPA, MHHPA, MTHPA, THPA, TCPA, HA and PMDA have been classified as sensitisers by inhalation and skin contact (39, 40). All of them have also been classified as irritants. In addition, PA and MA have been classified as harmful when swallowed because of the acute toxicity in animal studies. No occupational exposure limits for cyclic acid anhydrides have been set by the European Union.

14. Evaluation of human health risk

14.1 Groups at extra risk

When TCPA-exposed workers were investigated, smoking was found to interact with atopy in the production of specific IgE antibodies (185). On the other hand in a historical cohort study of TMA-exposed workers, there was an increased prevalence of sensitisation and work-related symptoms with increasing exposure but not with smoking or atopy (13). In another study, smoking was associated with specific IgE production to MTHPA only when the total IgE was low (200). In a prospective study of HHPA-, MHHPA-, and MTHPA-exposed workers an association was found between atopy and specific IgE antibodies. The effect of smoking was not significant (193).

In conclusion, atopy seems to predispose for sensitisation against cyclic acid anhydrides whereas no conclusion can be drawn with respect to smoking.

14.2 Assessment of health risk

The most common symptom from exposure to cyclic acid anhydrides is irritation of the mucous membranes (Tables 7 and 8). In long-term animal studies with MA, metaplasia of nasal tissue has been developed. Irritant nasal and ocular symptoms have been usual findings in industrial surveys (18, 130, 135, 214).

PA, TMA, MA, HHPA, MHHPA, MTHPA, TCPA, PMDA, HA and CA are capable of inducing IgE-mediated sensitisation followed by allergic diseases, e.g. allergic rhinitis often associated with allergic conjunctivitis and bronchial asthma (Table 10). The number of reports on MA, MHHPA, PMDA, HA or CA induced sensitisation is small. The prevalence of occupational asthma due to other cyclic anhydrides has varied between 2-39% in industrial surveys (203).

The allergic skin diseases caused by acid anhydrides include rare cases of IgE-mediated contact urticaria due to HHPA, MHHPA, MTHPA, MA and CA (83, 94, 95, 102, 174), and even more rare cases of allergic contact dermatitis of type IV allergy (57, 96).

Sensitisation and work related symptoms have been induced already at low levels of exposure, at 10-40 μg/m^3 for TMA, at 10-50 μg/m^3 for HHPA and MHHPA (mixed exposure in industrial surveys), and at 5-20 μg/m^3 for MTHPA. For PA and TCPA the corresponding exposure levels have been higher, 1 500-17 400 μg/m^3 and 140-590 μg/m^3, respectively (Table 12). The prevalence of sensitisation has increased with increasing exposure (Table 10).

When workers were exposed to a PA dust concentration of less than 100 μg/m^3, no asthmatics were found, but half of the workers had conjunctivitis and/or rhinitis (136). In a historical cohort study the exposure to PA or MA was found to be an uncommon cause of sensitisation at the low exposure levels measured, 8.9-11.9 μg/m^3 and 1.8-2.8 μg/m^3, respectively (13).

After reduction of TCPA exposure to less than 110 μg/m^3 no new cases of work-related asthma were reported (118). Lower concentrations, between 4.1-66.7 μg/m^3 of TCPA have, however, induced asthma reactions in challenge tests of sensitised workers with occupational asthma (184).

After the elimination or reduction of exposure, asthma has persisted although it has improved in some of the follow-up studies. Occupational rhinitis often precedes asthma, and therefore the early detection of rhinitis is important for the prevention of more severe bronchial asthma.

The severe pulmonary disease-anaemia syndrome due to TMA and PMDA with assumed high levels of exposure has been rare (29, 144, 212).

There are no reports on THPA induced work-related diseases.

SA injected subcutaneously has induced subcutaneous sarcomas in rats. IARC has stated that there is limited evidence for the animal carcinogenicity of SA and that it is not classifiable as carcinogen in humans (78).

14.3 Scientific basis for an occupational exposure limit

The data for setting occupational exposure limits is based on studies with information on dose-response effects. The number of the studies is limited, and some of them are not very recent. All cyclic anhydrides are considered irritants of the mucous membranes and skin.

Data on the main critical effects, sensitisation (specific IgE antibodies), and work-related symptoms (rhinoconjunctivitis and asthma) of PA, TMA, HHPA, MHHPA, MTHPA, and TCPA are compiled in Table 12 in relation to exposure levels. Occupational exposure limits for PA, TMA, and MA are presented in the Appendix.

The critical effects are as follows:

Methyl tetrahydrophthalic anhydride (MTHPA): irritation of mucous membranes of the eyes and airways and sensitisation-induced work-related diseases. Sensitisation, work-related rhinoconjunctivitis, and asthma have been verified for workers exposed to MTHPA levels of 5-20 μg/m^3.

Hexahydrophthalic anhydride (HHPA) and *Methyl hexahydrophthalic anhydride* (MHHPA): irritation of mucous membranes of the eyes and airways and sensitisation-induced work-related diseases. Sensitisation in workers exposed to HHPA levels of 10-50 μg/m^3 has been found.

Trimellitic anhydride (TMA): irritation of mucous membranes of the eyes and airways and sensitisation-induced work-related diseases. In a historical cohort study of 116 workers with TMA exposure at the level of 10-40 μg/m^3, sensitisation was found according to specific IgE antibodies, as were work-related respiratory symptoms.

Tetrachlorophthalic anhydride (TCPA): irritation of mucous membranes of the eyes and airways and sensitisation-induced work-related respiratory diseases. Exposure to TCPA concentrations of 140-590 μg/ m^3 has caused both sensitisation and work-related asthma. No new cases of work-related asthma have been reported after decreasing the exposure to less than 110 μg/m^3 (118). In challenge tests of a worker with TCPA asthma, a significant asthmatic response has been induced with concentrations between 4.1-66.7 μg/m^3 of TCPA.

Phthalic anhydride (PA): irritation of mucous membranes of the eyes and airways and sensitisation-induced work related diseases. Both work-related rhinoconjunc-tivitis and sensitisation, but no asthma, have been found in workers exposed to less than 100 μg/m^3 of PA.

Maleic anhydride (MA): irritation of mucous membranes of the eyes and airways and sensitisation-induced work-related diseases. Nasal metaplasia has been found in animal studies (1 100-9 800 μg/m^3 of MA). There is not enough data available for dose-response assessment in humans.

Tetrahydrophthalic anhydride (THPA): data insufficient for assessing the critical effect on humans.

Table 12. Critical effects (sensitisation and work-related symptoms) in man with corresponding exposure levels of cyclic acid anhydrides.

Acid anhydride	Exposure level (μg/m^3)	Critical effect	Reference
PA	1 500 –17 400	Sensitisation Asthma	(136)
TCPA	140-590	Sensitisation Work-related respiratory symptoms	(118)
TMA	10-40	Sensitisation Work-related respiratory symptoms	(13)
HHPA and MHHPA	10-50	Sensitisation	(195)
MTHPA	5-20	Sensitisation Rhinoconjunctivitis Asthma	(134, 202)

15. Research needs

Dose-response studies of several sensitising cyclic anhydrides are few or even lacking. Such studies are needed for assessing occupational exposure limits, especially since the sensitising properties of the cyclic anhydrides are not similar.

Furthermore follow-up studies are needed to determine the prognosis of asthma due to cyclic anhydrides.

Smoking and atopy as risk factors for sensitisation are not fully understood and need to be further investigated.

Assessing exposure when products manufactured from cyclic anhydrides are used in work processes is difficult. More knowledge is needed on the tasks expected to involve anhydrides as thermal degradation products.

Long-term inhalation studies on animals are needed to evaluate the carcinogenicity of acid anhydrides.

16. Summary

Keskinen H. *The Nordic Expert Group for Criteria Documentation of Health Risk from Chemicals and the Dutch Expert Committee on Occupational Standards*. 136. Cyclic acid anhydrides. Arbete och Hälsa 2004;15:1-74.

Cyclic acid anhydrides are widely used in the manufacture of resins and a variety of chemicals. Since the introduction of phthalic anhydride (PA) several new derivatives of cyclic acid anhydrides have came into use. Exposure to anhydrides occurs either in powder form or as fumes when anhydrides are used at elevated temperatures or when they are released as thermal degradation products. The technical product of a cyclic acid anhydride may contain other related anhydrides as impurities.

The critical effects of cyclic acid anhydrides are sensitisation, rhinoconjunctivitis and asthma. Occupational rhinoconjunctivitis and asthma due to cyclic acid anhydrides are usually IgE-mediated. Irritant work-related rhinoconjunctivitis is often found without sensitisation to anhydrides.

Allergic contact dermatitis due to anhydrides is rare.

The sensitising potency of cyclic acid anhydrides varies. According to limited data, trimellitic (TMA), hexahydrophthalic (HHPA), and methyl tetrahydrophthalic anhydride (MTHPA) are more sensitising than PA and tetrachlorophthalic anhydride (TCPA). Based on immunological cross-reactivity, the sensitising potency of methyl hexahydrophthalic anhydride (MHHPA) might be near that of HHPA and MTHPA. The level of exposure needed to cause specific IgE antibody production and work-related symptoms in mucous membranes and respiratory organs may be less than 10 μg/m^3 for the more highly sensitising anhydrides.

17. Summary in Swedish

Cykliska syraanhydrider har en utbredd användning vid tillverkning av hartser och en mängd andra kemikalier. Sedan ftalsyraanhydrid (PA) började användas har flera nya derivat av syraanhydrider kommit i bruk. Exponering för anhydrider sker antingen i form av pulver eller som rök när anhydriderna upphettas eller frigörs som termiska nedbrytningsprodukter. Den tekniska produkten av en cyklisk syraanhydrid kan innehålla liknande syraanhydrider som förorening.

De kritiska effekterna för cykliska syraanhydrider är sensibilisering, rinokonjunktivit och astma. Yrkesrelaterad rinokonjunktivit och astma till följd av syranhydrider är i regel IgE-medierade. Irritativ arbetsrelaterad rinokonjunktivit förekommer ofta utan föregående sensibilisering för syraanhydrider.

Allergiskt kontakteksem av syraanhydrider är sällsynt.

Sensibiliseringspotentialen hos de cykliska syraanhydriderna varierar. Enligt begränsade data är trimellitsyra- (TMA), hexahydroftalsyra- (HHPA) och metyltetrahydroftalsyraanhydrid (MTHPA) mer sensibiliserande än PA och tetraklorftalsyraanhydrid (TCPA). Baserat på immunologisk korsreaktivitet har metylhexahydroftalsyraanhydrid (MHHPA) likartad sensibiliseringspotential som HHPA och MTHPA. De exponeringsnivåer som erfordras för att ge specifikt IgE svar och arbetsrelaterade symtom på slemhinnor och andningsorgan kan vara lägre än 10 μg/m^3 för de mer kraftigt sensibiliserande syraanhydriderna.

Nyckelord: allergi, allergisk kontaktdermatit, astma, cykliska syraanhydrider, ftalsyraanhydrid, hygieniskt gränsvärde, hexahydroftalsyraanhydrid, irritation, konjunktivit, kontakturtikaria, maleinsyraanhydrid, metylhexahydroftalsyraanhydrid, metyltetrahydroftalsyraanhydrid, rinit, tetrahydroftalsyraanhydrid, tetrakloroftalsyraanhydrid, trimellitsyraanhydrid, trimellitsyraanhydrid-alveolit, yrkessjukdom.

18. References

1. ACGIH. *Documentation of the threshold limit values and biological exposure indices*. 7th ed. Cincinnati: American Conference of Governmental Industrial Hygienists Inc., 2001.

2. Ahmad D, Morgan WK, Patterson R, Williams T, Zeiss CR. Pulmonary haemorrhage and haemolytic anaemia due to trimellitic anhydride. *Lancet* 1979;2:328-330.

3. Amoore JE, Hautala E. Odor as an aid to chemical safety: Odor thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. *J Appl Toxicol* 1983;3:272-290.

4. Andius P, Arakawa H, Molne J, Pullerits T, Skoogh BE, Lötvall J. Inflammatory responses in skin and airways after allergen challenge in brown Norway rats sensitized to trimellitic anhydride. *Allergy* 1996;51:556-562.

5. Arakawa H, Andius P, Kawikova I, Skoogh BE, Löfdahl CG, Lötvall J. Treatment with cyclosporin A during sensitization with trimellitic anhydride attenuates the airway responses to allergen challenge three weeks later. *Eur J Pharmacol* 1994;252:313-319.

6. Arakawa H, Kawikova I, Skoogh BE, Hayes J, Morikawa A, Löfdahl CG, Lötvall J. Role of arachidonic acid metabolites in airway responses induced by trimellitic anhydride in actively sensitized guinea pigs. *Am Rev Respir Dis* 1993;147:1116-1121.

7. Arakawa H, Lötvall J, Kawikova I, Tee R, Hayes J, Löfdahl CG, Taylor AJ, Skoogh BE. Airway allergy to trimellitic anhydride in guinea pigs: different time courses of IgG1 titer and airway responses to allergen challenge. *J Allergy Clin Immunol* 1993;92:425-434.

8. Arakawa H, Lötvall J, Linden A, Kawikova I, Löfdahl CG, Skoogh BE. Role of eicosanoids in airflow obstruction and airway plasma exudation induced by trimellitic anhydride-conjugate in guinea-pigs 3 and 8 weeks after sensitization. *Clin Exp Allergy* 1994;24:582-589.

9. Arts JH, Dröge SC, Spanhaak S, Bloksma N, Penninks AH, Kuper CF. Local lymph node activation and IgE responses in brown Norway and Wistar rats after dermal application of sensitizing and non-sensitizing chemicals. *Toxicology* 1997;117:229-234.

10. Arts JH, Kuper CF, Spoor SM, Bloksma N. Airway morphology and function of rats following dermal sensitization and respiratory challenge with low molecular weight chemicals. *Toxicol Appl Pharmacol* 1998;152:66-76.

11. Baader EW. Erkrankungen durch Phthalsäure und ihre Verbindungen. *Arch Gewerbepathol Gewerbehyg* 1955;13:419-453.

12. Barker RD, Harris JM, Welch JA, Venables KM, Newman Taylor AJ. Occupational asthma caused by tetrachlorophthalic anhydride: a 12-year follow-up. *J Allergy Clin Immunol* 1998;101:717-719.

13. Barker RD, van Tongeren MJ, Harris JM, Gardiner K, Venables KM, Newman Taylor AJ. Risk factors for sensitisation and respiratory symptoms among workers exposed to acid anhydrides: a cohort study. *Occup Environ Med* 1998;55:684-691.

14. Barker RD, van Tongeren MJ, Harris JM, Gardiner K, Venables KM, Newman Taylor AJ. Risk factors for bronchial hyperresponsiveness in workers exposed to acid anhydrides. *Eur Respir J* 2000;15:710-715.

15. Batyrova T, Uzhdavini E. The toxicology of trimellitic acid and trimellitic anhydride. Tr. Nauchno-Issled. Inst. *Neftekhim Proizvodstr* 1970;2:149-154.

16. Baur X. Asthmatic reactions after nasal allergen provocation. *Respiration* 1996;63:84-87.

17. Baur X, Czuppon A. Diagnostic validation of specific IgE antibody concentrations, skin prick testing, and challenge tests in chemical workers with symptoms of sensitivity to different anhydrides. *J Allergy Clin Immunol* 1995;96:489-494.

18. Baur X, Czuppon AB, Rauluk I, Zimmermann FB, Schmitt B, Egen-Korthaus M, Tenkhoff N, Degens PO. A clinical and immunological study on 92 workers occupationally exposed to anhydrides. *Int Arch Occup Environ Health* 1995;67:395-403.

19. Bernstein DI, Patterson R, Zeiss CR. Clinical and immunologic evaluation of trimellitic anhydride-and phthalic anhydride-exposed workers using a questionnaire with comparative analysis of enzyme-linked immunosorbent and radioimmunoassay studies. *J Allergy Clin Immunol* 1982;69:311-318.

20. Bernstein DI, Roach DE, McGrath KG, Larsen RS, Zeiss CR, Patterson R. The relationship of airborne trimellitic anhydride concentrations to trimellitic anhydride--induced symptoms and immune responses. *J Allergy Clin Immunol* 1983;72:709-713.

21. Biagini RE, Bernstein DI, Gallagher JS, Moorman WJ, Knecht EA, Smallwood AW, Bernstein IL. Immune responses of cynomolgus monkeys to phthalic anhydride. *J Allergy Clin Immunol* 1988;82:23-29.

22. Botham PA, Rattray NJ, Woodcock DR, Walsh ST, Hext PM. The induction of respiratory allergy in guinea-pigs following intradermal injection of trimellitic anhydride: a comparison with the response to 2,4-dinitrochlorobenzene. *Toxicol Lett* 1989;47:25-39.

23. Bourret J, Gauthier G, Roche L. Intoxication par l'anhydride phthalique. *Acta Med Leg Soc* 1950;3:33-37.

24. Budavari S, O'Neil MJ, Smith A, Heckelman PE, Kinneary JF. *The Merck Index*. 12th ed. Whitehouse Station, New Jersey: Merck & Co., Inc., 1996: 1741.

25. Chandler MJ, Zeiss CR, Leach CL, Hatoum NS, Levitz D, Garvin PJ, Patterson R. Levels and specificity of antibody in bronchoalveolar lavage (BAL) and serum in an animal model of trimellitic anhydride-induced lung injury. *J Allergy Clin Immunol* 1987;80:223-229.

26. Chee CB, Lee HS, Cheong TH, Wang YT, Poh SC. Occupational asthma due to hexahydro-phthalic anhydride: a case report. *Br J Ind Med* 1991;48:643-645.

27. Chester EH, Schwartz HJ, Payne CB, Jr., Greenstein S. Phthalic anhydride asthma. *Clin Allergy* 1977;7:15-20.

28. Cui ZH, Sjöstrand M, Pullerits T, Andius P, Skoogh BE, Lötvall J. Bronchial hyper-responsiveness, epithelial damage, and airway eosinophilia after single and repeated allergen exposure in a rat model of anhydride-induced asthma. *Allergy* 1997;52:739-746.

29. Czuppon AB, Kaplan V, Speich R, Baur X. Acute autoimmune response in a case of pyromellitic acid dianhydride-induced hemorrhagic alveolitis. *Allergy* 1994;49:337-341.

30. Dearman RJ, Hegarty JM, Kimber I. Inhalation exposure of mice to trimellitic anhydride induces both IgG and IgE anti-hapten antibody. *Int Arch Allergy Appl Immunol* 1991;95:70-76.

31. Dearman RJ, Kimber I. Differential stimulation of immune function by respiratory and contact chemical allergens. *Immunology* 1991;72:563-570.

32. Dearman RJ, Kimber I. Divergent immune responses to respiratory and contact chemical allergens: antibody elicited by phthalic anhydride and oxazolone. *Clin Exp Allergy* 1992;22:241-250.

33. Dearman RJ, Warbrick EV, Humphreys IR, Kimber I. Characterization in mice of the immunological properties of five allergenic acid anhydrides. *J Appl Toxicol* 2000;20:221-230.

34. Deutsche Forschungsgemeinschaft (DFG). Gesundheitsschlädische arbeitsstoffe. *Toxiko-logisch-Arbeitsmedizinische Begründung von MAK-Werten*. Weinheim: Wiley VCH., 1986/1987.

35. Drexler H, Schaller KH, Nielsen J, Weber A, Weihrauch M, Welinder H, Skerfving S. Efficacy of measures of hygiene in workers sensitised to acid anhydrides and the influence of selection bias on the results. *Occup Environ Med* 1999;56:202-205.

36. Drexler H, Weber A, Letzel S, Kraus G, Schaller KH, Lenhert G. Detection and clinical relevance of a type I allergy with occupational exposure to hexahydrophthalic anhydride and methyltetrahydrophthalic anhydride. *Int Arch Occup Environ Health* 1994;65:279-283.

37. Durham SR, Graneek BJ, Hawkins R, Taylor AJ. The temporal relationship between increases in airway responsiveness to histamine and late asthmatic responses induced by occupational agents. *J Allergy Clin Immunol* 1987;79:398-406.

38. Dykewicz MS, Patterson R, Harris KE. Induction of antigen-specific bronchial reactivity to trimellityl-human serum albumin by passive transfer of serum from humans to rhesus monkeys. *J Lab Clin Med* 1988;111:459-465.

39. European commission (EC). Commission Directive 98/73/EC. *Official Journal of the European Community*. 1998; L 305, 16.11.98.

40. European commission (EC). Commission Directive 98/98/EC. *Official Journal of the European Community*. 1998; L 355, 30.12.1998.

41. Fabro S, Shull G, Brown NA. The relative teratogenic index and teratogenic potency: proposed components of developmental toxicity risk assessment. *Teratog Carcinog Mutagen* 1982;2:61-76.

42. Falbe J, Regitz M. *Römpp Lexikon: Chemie A-Z*. 10th ed. Stuttgart, New York: Georg Thieme Verlag, 1999.

43. Fawcett IW, Taylor AJ, Pepys J. Asthma due to inhaled chemical agents--epoxy resin systems containing phthalic acid anhydride, trimellitic acid anhydride and triethylene tetramine. *Clin Allergy* 1977;7:1-14.

44. Flaherty DK, Gross CJ, Winzenburger P, Compas MB, McGarity K, Tillman E. In vitro immunologic studies on a population of workers exposed to phthalic and tetrachlorophthalic anhydride. *J Occup Med* 1988;30:785-790.

45. Frans A, Pahulycz C. [Transient syndrome of acute irritation of the bronchi induced by single and massive inhalation of phthalic anhydride]. *Rev Pneumol Clin* 1993;49:247-251.

46. Fraser DG, Regal JF, Arndt ML. Trimellitic anhydride-induced allergic response in the lung: role of the complement system in cellular changes. *J Pharmacol Exp Ther* 1995;273:793-801.

47. Gad S, Walsh R, Dunn B. Correlation of ocular and dermal irritancy of industrial chemicals. *J Toxicol Cut Ocular Toxicol* 1986;5:195-213.

48. Gad SC. A scheme for the prediction and ranking of relative potencies of dermal sensitizers based on data from several systems. *J Appl Toxicol* 1988;8:361-368.

49. Galloway SM, Armstrong MJ, Reuben C, Colman S, Brown B, Cannon C, Bloom AD, Nakamura F, Ahmed M, Duk S, Rimpo J, Margolin B, Reshnick M, Anderson B, Zeiger E. Chromosome aberrations and sister chromatid exchanges in Chinese hamster ovary cells: evaluations of 108 chemicals. *Environ Mol Mutagen* 1987;10:1-175.

50. Gannon PF, Sherwood Burge P, Hewlett C, Tee RD. Haemolytic anaemia in a case of occupational asthma due to maleic anhydride. *Br J Ind Med* 1992;49:142-143.

51. Gautrin D, Bernstein IL, Brooks S. Reactive airways dysfunction syndrome or irritant-induced asthma. In: Bernstein IL, Chang-Yeung M, Malo, J-L, Bernstein DI, eds. *Asthma in the Workplace*. 2nd ed. New York, Basel: Marcel Dekker Inc., 1999:565-593.

52. Gerhardsson L, Grammer LC, Shaughnessy MA, Patterson R. IgG subclass antibody against trimellitic anhydride in workers with and without immunologic lung diseases. *J Occup Med* 1992;34:989-992.

53. Gerhardsson L, Grammer LC, Shaughnessy MA, Patterson R. Immunologic specificity of IgG against trimellityl-human serum albumin in serum samples of workers exposed to trimellitic anhydride. *J Lab Clin Med* 1993;121:792-796.

54. Gervais P, Efthymiou L, Hebert S, Diamant-Berger O. [Diagnosis and physiopathology of asthma due to phthalic anhydride: value of the lymphoblastic transformation test]. *Eur J Toxicol* 1972;5:106-109.

55. Geyer R, Jones RC, Mezin N. Determination of trimellitic anhydride in workplace air using reverse phase high performance liquid chromatography. *J High Res Chromatogr* 1986;9:308-309.

56. Geyer R, Saunders GA. Determination of maleic anhydride in workplace air by reversed-phase high-performance liquid chromatography. *J Chromatogr* 1986;368:456-458.

57. Goransson K. Allergic contact dermatitis to an epoxy hardener: dodecenyl-succinic anhydride. *Contact Dermatitis* 1977;3:277-278.

58. Grammer L, Shaughnessy M, Kenamore B. Utility of antibody in identifying individuals who have or will develop anhydride-induced respiratory disease. *Chest* 1998;114:1199-1202.

59. Grammer LC, Shaughnessy MA. Study of employees with anhydride-induced respiratory disease after removal from exposure. *J Occup Environ Med* 1996;38:771-774.

60. Grammer LC, Shaughnessy MA, Henderson J, Zeiss CR, Kavich DE, Collins MJ, Pecis KM, Kenamore BD. A clinical and immunologic study of workers with trimellitic-anhydride-induced immunologic lung disease after transfer to low exposure jobs. *Am Rev Respir Dis* 1993;148:54-57.

61. Grammer LC, Shaughnessy MA, Lowenthal M. Hemorrhagic rhinitis. An immunologic disease due to hexahydrophthalic anhydride. *Chest* 1993;104:1792-1794.

62. Grammer LC, Shaughnessy MA, Lowenthal M, Yarnold PR. Risk factors for immuno-logically mediated respiratory disease from hexahydrophthalic anhydride. *J Occup Med* 1994;36:642-646.

63. Grammer LC, Shaughnessy MA, Yarnold PR. Risk factors for immunologically mediated disease in workers with respiratory symptoms when exposed to hexahydrophthalic anhydride. *J Lab Clin Med* 1996;127:443-447.

64. Guerin JC, Deschamps O, Guillot YL, Chavaillon JM, Kalb JC. [A case of asthma due to maleic anhydride (author's transl)]. *Poumon Coeur* 1980;36:393-395.

65. Haseman JK, Huff JE, Zeiger E, McConnell EE. Comparative results of 327 chemical carcinogenicity studies. *Environ Health Perspect* 1987;74:229-235.

66. Hatanaka S, Imamura I, Terazawa Y, Kuroda K, Endo G. The characteristics of specific IgG to phthalic anhydride (PA)-albumin conjugate. *Ind Health* 1997;35:508-514.

67. Hayes JP, Barnes PJ, Taylor AJ, Chung KF. Effect of a topical corticosteroid on airway hyperresponsiveness and eosinophilic inflammation induced by trimellitic anhydride exposure in sensitized guinea pigs. *J Allergy Clin Immunol* 1993;92:450-456.

68. Hayes JP, Daniel R, Tee RD, Barnes PJ, Taylor AJ, Chung KF. Bronchial hyperreactivity after inhalation of trimellitic anhydride dust in guinea pigs after intradermal sensitization to the free hapten. *Am Rev Respir Dis* 1992;146:1311-1314.

69. Hayes JP, Kuo HP, Rohde JA, Newman Taylor AJ, Barnes PJ, Chung KF, Rogers DF. Neurogenic goblet cell secretion and bronchoconstriction in guinea pigs sensitised to trimellitic anhydride. *Eur J Pharmacol* 1995;292:127-134.

70. Hayes JP, Lötvall JO, Baraniuk J, Daniel R, Barnes PJ, Taylor AJ, Chung KF. Broncho-constriction and airway microvascular leakage in guinea pigs sensitized with trimellitic anhydride. *Am Rev Respir Dis* 1992;146:1306-1310.

71. Hayes JP, Lötvall JO, Barnes PJ, Newman Taylor AJ, Chung KF. Involvement of inflam-matory mediators in the airway responses to trimellitic anhydride in sensitized guinea-pigs. *Br J Pharmacol* 1992;106:828-832.

72. Hazelden KP. *Screening of priority chemicals for reproductive hazards*. NIOSH contract no. 219-81-6005, 1983:1-127.

73. Henriks-Eckerman M, Engström B, Ånäs E. Thermal degradation products of steel protective paints. *Am Ind Hyg Assoc J* 1990:241-244.

74. Herbert FA, Orford R. Pulmonary hemorrhage and edema due to inhalation of resins contain-ing tri-mellitic anhydride. *Chest* 1979;76:546-551.

75. Hilliard CA, Armstrong MJ, Bradt CI, Hill RB, Greenwood SK, Galloway SM. Chromosome aberrations in vitro related to cytotoxicity of nonmutagenic chemicals and metabolic poisons. *Environ Mol Mutagen* 1998;31:316-326.

76. Howe W, Venables KM, Topping MD, Dally MB, Hawkins R, Law JS, Taylor AJ. Tetrachlorophthalic anhydride asthma: evidence for specific IgE antibody. *J Allergy Clin Immunol* 1983;71:5-11.

77. IARC. Succinic anhydride. *IARC monographs on the evaluation of carcinogenic risks to humans*. Vol. 15. Lyon: International Agency for Research on Cancer, 1977:265-271.

78. IARC. *IARC monographs on the evaluation of carcinogenic risks to humans*. Suppl. 7. Lyon: International Agency for Research on Cancer, 1987.

79. IARC. *IARC monographs on the evaluation of carcinogenic risks to humans*. Vol. 48. Lyon: International Agency for Research on Cancer, 1990.

80. IPCS. The International Programme on Chemical Safety. Environmental Health Criteria 185. *Chlorendic acid and anhydride*. Geneva: World Health Organization, 1996:74.

81. Jackson J, Jones AH. Comments on: Br J Ind Med 1992;49:142-143. Gannon P F, Sherwood Burge P, Hewlett C, Tee RD. Haemolytic anaemia in a case of occupational asthma due to maleic anhydride. *Br J Ind Med* 1993;50:191-192.

82. Johyama Y, Yokota K, Fujiki Y, Takeshita T, Morimoto K. Determination of methyltetra-hydrophthalic anhydride in air using gas chromatography with electron-capture detection. *Ind Health* 1999;37:364-368.

83. Jolanki R, Estlander T, Kanerva L. Occupational contact dermatitis and contact urticaria caused by epoxy resins. *Acta Derm Venereol Suppl* 1987;134:90-94.

84. Jönsson B, Lindh C. Determination of hexahydrophthalic and methylhexahydrophthalic acids in urine by gas chromatography-negative-ion chemical-ionisation mass spectrometry. *Chromatographia* 1996;42:647-652.

85. Jönsson B, Lindh C, Welinder H. Haemoglobin adducts and specific immunoglobulin G in humans as biomarkers of exposure to hexahydrophthalic anhydride. *Biomarkers* 1997;2:239-246.

86. Jönsson B, Skarping G. Method for the biological monitoring of hexahydrophthalic anhydride by the determination of hexahydrophthalic acid in urine using gas chromatography and selected-ion monitoring. *J Chromatogr* 1991;572:117-131.

87. Jönsson B, Welinder H, Pfäffli P. Determination of cyclic organic acid anhydrides in air using gas chromatography .1. A review. *Analyst* 1996;121:1279-1284.

88. Jönsson B, Welinder H, Skarping G. Determination of hexahydrophthalic anhydride in air using gas chromatography. *J Chromatogr* 1991;558:247-256.

89. Jönsson B, Welinder H, Skarping G. Hexahydrophthalic acid in urine as an index of exposure to hexahydrophthalic anhydride. *Int Arch Occup Environ Health* 1991;63:77-79.

90. Jönsson BA, Skerfving S. Toxicokinetics and biological monitoring in experimental exposure of humans to gaseous hexahydrophthalic anhydride. *Scand J Work Environ Health* 1993;19:183-190.

91. Jönsson BA, Welinder H, Hansson C, Ståhlbom B. Occupational exposure to hexahydro-phthalic anhydride: air analysis, percutaneous absorption, and biological monitoring. *Int Arch Occup Environ Health* 1993;65:43-47.

92. Jönsson BA, Wishnok JS, Skipper PL, Stillwell WG, Tannenbaum SR. Lysine adducts between methyltetrahydrophthalic anhydride and collagen in guinea pig lung. *Toxicol Appl Pharmacol* 1995;135:156-162.

93. Jönsson BAG, Lindh C, Gustavsson CA, Welinder H, Pfäffli P. Determination of cyclic organic acid anhydrides in air using gas chromatography. 2. Sampling and determination of hexahydrophthalic anhydride, methylhexahydrophthalic anhydride, tetrahydrophthalic anhydride and octenylsuccinic anhydride. *Analyst* 1996;121:1285-1290.

94. Kanerva L, Alanko K. Occupational allergic contact urticaria from maleic anhydride. *Contact Dermatitis* 2000;42:170-172.

95. Kanerva L, Alanko K, Jolanki R, Estlander T. Airborne allergic contact urticaria from methylhexahydrophthalic anhydride and hexahydrophthalic anhydride. *Contact Dermatitis* 1999;41:339-341.

96. Kanerva L, Hyry H, Jolanki R, Hytonen M, Estlander T. Delayed and immediate allergy caused by methylhexahydrophthalic anhydride. *Contact Dermatitis* 1997;36:34-38.

97. Karjalainen A, Aalto L, Jolanki R, Keskinen H, Savela A. *Ammattitaudit 1997*. Helsinki: Finnish Institute of Occupational Health, 1998. (Article in Finnish).

98. Karjalainen A, Aalto L, Jolanki R, Keskinen H, Paakkulainen H, Savela A. *Ammattitaudit 1998*. Helsinki: Finnish Institute of Occupational Health, 1999. (Article in Finnish).

99. Karjalainen A, Aalto L, Jolanki R, Keskinen H, Mäkinen I, Savela A. *Occupational diseases in Finland in 1999*. Helsinki: Finnish Institute of Occupational Health, 2001.

100. Kern RA. Asthma and allergic rhinitis due to sensitization to phthalic anhydride. *J Allergy* 1939;10:164-165.

101. Keskinen H. Organic acid anhydrides. In: Beije B, Lundberg P, eds. *Criteria document from the Nordic Expert Group*. Solna: National Institute of Occupational Health, Arbete och Hälsa 1991;2:129-188.

102. Keskinen H, Pfäffli P, Pelttari M, Tupasela O, Tuomi T, Tuppurainen M, Hameila M, Kanerva L, Nordman H. Chlorendic anhydride allergy. *Allergy* 2000;55:98-99.

103. Kluwe WM. Carcinogenic potential of phthalic acid esters and related compounds: structure-activity relationships. *Environ Health Perspect* 1986;65:271-278.

104. Kluwe WM, McConnell EE, Huff JE, Haseman JK, Douglas JF, Hartwell WV. Carcinogenicity testing of phthalate esters and related compounds by the National Toxicology Program and the National Cancer Institute. *Environ Health Perspect* 1982;45:129-133.

105. Korhonen A, Hemminki K, Vainio H. Embryotoxic effects of phtalic acid derivatives, phosphates and aromatic oils used in the manufacturing of rubber on three day chicken embryos. *Drug Chem Toxicol* 1983;6:191-207.

106. Leach CL, Hatoum NS, Ratajczak HV, Zeiss CR, Garvin PJ. Evidence of immunologic control of lung injury induced by trimellitic anhydride. *Am Rev Respir Dis* 1988;137:186-190.

107. Leach CL, Hatoum NS, Ratajczak HV, Zeiss CR, Roger JC, Garvin PJ. The pathologic and immunologic response to inhaled trimellitic anhydride in rats. *Toxicol Appl Pharmacol* 1987;87:67-80.

108. Lee HS, Wang YT, Cheong TH, Tan KT, Chee BE, Narendran K. Occupational asthma due to maleic anhydride. *Br J Ind Med* 1991;48:283-285.

109. Letz G, Wugofski L, Cone JE, Patterson R, Harris KE, Grammer LC. Trimellitic anhydride exposure in a 55-gallon drum manufacturing plant: clinical, immunologic, and industrial hygiene evaluation. *Am J Ind Med* 1987;12:407-417.

110. Levy SA, Storey J, Phashko BE. Meat worker's asthma. *J Occup Med* 1978;20:116-118.

111. Lewis RJ, Sr. *Sax´s Dangerous properties of industrial materials*. 9th ed. New York: Van Nostrand Reinhold Co., 1996.

112. Lindh CH, Jönsson BA. Method for analysis of methyltetrahydrophthalic acid in urine using gas chromatography and selected ion monitoring. *J Chromatogr B Biomed Appl* 1994;660:57-66.

113. Lindh CH, Jönsson BA. Determination of hexahydrophthalic acid and methylhexahydrophthalic acid in plasma after derivatisation with pentafluorobenzyl bromide using gas chromatography and mass spectrometric detection. *J Chromatogr B Biomed Sci Appl* 1997;691:331-339.

114. Lindh CH, Jönsson BA. Quantification method of human hemoglobin adducts from hexahydrophthalic anhydride and methylhexahydrophthalic anhydride. *J Chromatogr B Biomed Sci Appl* 1998;710:81-90.

115. Lindh CH, Jönsson BA, Johannesson G, Zhang XD, Welinder H, Brittebo EB. Binding of the potent allergen hexahydrophthalic anhydride in the mucosa of the upper respiratory and alimentary tract following single inhalation exposures in guinea pigs and rats. *Toxicology* 1999;134:153-168.

116. Lindh CH, Jönsson BA, Welinder H. Biological monitoring of methylhexahydrophthalic anhydride by determination of methylhexahydrophthalic acid in urine and plasma from exposed workers. *Int Arch Occup Environ Health* 1997;70:128-132.

117. Lindh CH, Jönsson BA, Welinder HE. Direct measurement of hexahydrophthalic anhydride in workplace air with a transportable Fourier transform infrared spectrometer. *Am Ind Hyg Assoc J* 1996;57:832-836.

118. Liss GM, Bernstein D, Genesove L, Roos JO, Lim J. Assessment of risk factors for IgE-mediated sensitization to tetrachlorophthalic anhydride. *J Allergy Clin Immunol* 1993;92:237-247.

119. Lowenthal M, Shaughnessy MA, Harris KE, Grammer LC. Immunologic cross-reactivity of acid anhydrides with immunoglobulin E against trimellityl-human serum albumin. *J Lab Clin Med* 1994;123:869-873.

120. Maccia CA, Bernstein IL, Emmett EA, Brooks SM. In vitro demonstration of specific IgE in phthalic anhydride hypersensitivity. *Am Rev Respir Dis* 1976;113:701-704.

121. Macgregor JT, Friedman M. Nonmutagenicity of tetrabromophthalic anhydride and tetrabromophthalic acid in the ames Salmonella/microsome mutagenicity test. *Mutat Res* 1977;56:81-84.

122. Malten KE, Zielhuis RL. *Industrial toxicology and dermatology in the production and processing of plastics. Elsevier monographs on toxic agents.* Amsterdam, London, New York: Elsevier publishing company, 1964.

123. Mazur G, Pethran A. Detection of specific IgE in isocyanate and phthalic anhydride exposed workers: comparison of RAST RIA, Immuno CAP System FEIA, and Magic Lite SQ. *Allergy* 1993;48:627-630.

124. McGrath KG, Roach D, Zeiss CR, Patterson R. Four-year evaluation of workers exposed to trimellitic anhydride. A brief report. *J Occup Med* 1984;26:671-675.

125. Meadway J. Asthma and atopy in workers with an epoxy adhesive. *Br J Dis Chest* 1980;74:149-154.

126. Menschick H. Gesundheitliche Gefahren bei der Herstellung von Phthalsäureanhydrid. *Arch Gewerbepathol Gewerbehyg* 1955;13:454-475.

127. Moller DR, Gallagher JS, Bernstein DI, Wilcox TG, Burroughs HE, Bernstein IL. Detection of IgE-mediated respiratory sensitization in workers exposed to hexahydrophthalic anhydride. *J Allergy Clin Immunol* 1985;75:663-672.

128. Moscato G, Gherson G, Salvaterra A, Vidi I. [Nasal and bronchial respiratory pathology in a group of workers exposed to phthalic anhydride]. *G Ital Med Lav* 1986;8:57-64.

129. Motolese A, Truzzi M, Giannini A, Seidenari S. Contact dermatitis and contact sensitization among enamellers and decorators in the ceramics industry. *Contact Dermatitis* 1993;28:59-62.

130. Nielsen J, Bensryd I, Almquist H, Dahlqvist M, Welinder H, Alexandersson R, Skerfving S. Serum IgE and lung function in workers exposed to phthalic anhydride. *Int Arch Occup Environ Health* 1991;63:199-204.

131. Nielsen J, Fahraeus C, Bensryd I, Akesson B, Welinder H, Linden K, Skerfving S. Small airways function in workers processing polyvinylchloride. *Int Arch Occup Environ Health* 1989;61:427-430.

132. Nielsen J, Johnson U, Welinder H, Bensryd I, Rylander L, Skerfving S. HLA and immune nonresponsiveness in workers exposed to organic acid anhydrides. *J Occup Environ Med* 1996;38:1087-1090.

133. Nielsen J, Welinder H, Bensryd I, Andersson P, Skerfving S. Symptoms and immunologic markers induced by exposure to methyltetrahydrophthalic anhydride. *Allergy* 1994;49:281-286.

134. Nielsen J, Welinder H, Horstmann V, Skerfving S. Allergy to methyltetrahydrophthalic anhydride in epoxy resin workers. *Br J Ind Med* 1992;49:769-775.

135. Nielsen J, Welinder H, Ottosson H, Bensryd I, Venge P, Skerfving S. Nasal challenge shows pathogenetic relevance of specific IgE serum antibodies for nasal symptoms caused by hexahydrophthalic anhydride. *Clin Exp Allergy* 1994;24:440-449.

136. Nielsen J, Welinder H, Schutz A, Skerfving S. Specific serum antibodies against phthalic anhydride in occupationally exposed subjects. *J Allergy Clin Immunol* 1988;82:126-133.

137. Nielsen J, Welinder H, Skerfving S. Allergic airway disease caused by methyl tetrahydro-phthalic anhydride in epoxy resin. *Scand J Work Environ Health* 1989;15:154-155.

138. NIOSH. *Manual of analytical methods*. 4th ed. Cincinnati: US National Institute for Occupational Safety and Health, 1994.

139. NIOSH. *Registry of Toxic Effects of Chemical Substances (RTECS)*. US National Institute for Occupational Safety and Health, 2001.

140. NLM. *Hazardous Substances Databank (HSDB)*. Bethesda, MD: US National Library of Medicine, 1999.

141. Palacian E, Gonzalez PJ, Pineiro M, Hernandez F. Dicarboxylic acid anhydrides as dissociating agents of protein-containing structures. *Mol Cell Biochem* 1990;97:101-111.

142. Patterson R, Addington W, Banner AS, Byron GE, Franco M, Herbert FA, Nicotra MB, Pruzansky JJ, Rivera M, Roberts M, Yawn D, Zeiss CR. Antihapten antibodies in workers exposed to trimellitic anhydride fumes: a potential immunopathogenetic mechanism for the trimellitic anhydride pulmonary disease--anemia syndrome. *Am Rev Respir Dis* 1979;120:1259-1267.

143. Patterson R, Roberts M, Zeiss CR, Pruzansky JJ. Human antibodies against trimellityl proteins: comparison of specificities of IgG, IgA and IgE classes. *Int Arch Allergy Appl Immunol* 1981;66:332-340.

144. Patterson R, Zeiss CR, Pruzansky JJ. Immunology and immunopathology of trimellitic anhydride pulmonary reactions. *J Allergy Clin Immunol* 1982;70:19-23.

145. Patterson R, Zeiss CR, Roberts M, Pruzansky JJ, Wolkonsky P, Chacon R. Human antihapten antibodies in trimellitic anhydride inhalation reactions. Immunoglobulin classes of anti-trimellitic anhydride antibodies and hapten inhibition studies. *J Clin Invest* 1978;62:971-978.

146. Pfäffli P. Phthalic acid excretion as an indicator of exposure to phthalic anhydride in the work atmosphere. *Int Arch Occup Environ Health* 1986;58:209-216.

147. Pfäffli P. Phthalic anhydride as an impurity in industrial atmospheres: assay in air samples by gas chromatography with electron-capture detection. *Analyst* 1986;111:813-817.

148. Pfäffli P. Determination of low concentrations of trimellitic anhydride in air. *J Chromatogr* 1994;684:269-275.

149. Pfäffli P. Sampling of airborne combustion fume for chemical analysis: Application to determination of phthalic anhydride in condensed powder paint fume. *Staub Reinhalt Luft* 1994;54:403-407.

150. Pfäffli P, Savolainen H. Determination of 4-methyl-cis-hexahydrophthalic anhydride in human blood by gas chromatography with electron-capture detection. *Analyst* 1991;116:1333-1336.

151. Pfäffli P, Savolainen H, Keskinen H. Determination of carboxylic acids in biological samples as their trichloroethyl esters by gas chromatography. *Chromatographia* 1989;27:483-488.

152. Phillips BJ, Anderson D, Gangolli SD. Studies on the genetic effects of phthalic acid esters on cells in culture. *Environ Health Perspect* 1986;65:263-266.

153. Piirila P, Keskinen H, Anttila S, Hyvonen M, Pfaffli P, Tuomi T, Tupasela O, Tuppurainen M, Nordman H. Allergic alveolitis following exposure to epoxy polyester powder paint containing low amounts (<1%) of acid anhydrides. *Eur Respir J* 1997;10:948-951.

154. Potokar M, Grundler OJ, Heusener A, Jung R, Murmann P, Schobel C, Suberg H, Zechel HJ. Studies on the design of animal tests for the corrosiveness of industrial chemicals. *Food Chem Toxicol* 1985;23:615-617.

155. Pullerits T, Dahlgren U, Skoogh BE, Lötvall J. Development of antigen-specific IgE after sensitisation with trimellitic anhydride in rats is attenuated by glucocorticoids and cyclosporin A. *Int Arch Allergy Immunol* 1997;112:279-286.

156. Riboli E, Bai E, Berrino F, Merisi A. Mortality from lung cancer in an acetylene and phthalic anhydride plant. A case-referent study. *Scand J Work Environ Health* 1983;9:455-462.

157. Rice DL, Jenkins DE, Gray JM. Chemical pneumonitis secondary to inhalation of epoxy pipe coating. *Arch Environ Health* 1977;32:173-178.

158. Ridgway P, Morris L, Ogunbiyi AO, Brown RH, Cocker J. *Acid anhydrides. Criteria document for an occupational exposure limit*. HSE Books. London: UK Health and Safety Executive, 1996:73.

159. Ridley WP, Warren J, Nair RS. Effect of tetrachlorophthalic anhydride on hepatic microsomal metabolism in rats and mice. *J Toxicol Environ Health* 1988;24:217-227.

160. Rosenman KD, Bernstein DI, O'Leary K, Gallagher JS, D'Souza L, Bernstein IL. Occupational asthma caused by himic anhydride. *Scand J Work Environ Health* 1987;13:150-154.

161. Rosqvist S, Johannesson G, Lindh CH, Jonsson BA. Quantification of protein adducts of hexahydrophthalic anhydride and methylhexahydrophthalic anhydride in human plasma. *J Environ Monit* 2000;2:155-160.

162. Ruth JH. Odor thresholds and irritation levels of several chemical substances: a review. *Am Ind Hyg Assoc J* 1986;47:142-151.

163. Sala E, Hytonen M, Tupasela O, Estlander T. Occupational laryngitis with immediate allergic or immediate type specific chemical hypersensitivity. *Clin Otolaryngol* 1996;21:42-48.

164. Sale SR, Roach DE, Zeiss CR, Patterson R. Clinical and immunologic correlations in trimellitic anhydride airway syndromes. *J Allergy Clin Immunol* 1981;68:188-193.

165. Sarlo K, Clark ED, Ferguson J, Zeiss CR, Hatoum N. Induction of type I hypersensitivity in guinea pigs after inhalation of phthalic anhydride. *J Allergy Clin Immunol* 1994;94:747-756.

166. Savolainen H, Pfaffli P. Biochemical effects and monitoring of exposure of rats to 4-methylcyclohexyl-1,6-dicarboxylic acid anhydride vapour. *Acta Pharmacol Toxicol (Copenh)* 1986;59:209-213.

167. Sax NI, Lewis RJ Sr. *Hawley's condensed chemical dictionary*. New York: Van Nostrand Reinhold Co., 1987:1288.

168. Schlueter DP, Banaszak EF, Fink JN, Barboriak J. Occupational asthma due to tetrachlorophthalic anhydride. *J Occup Med* 1978;20:183-188.

169. Shelby MD, Stasiewicz S. Chemicals showing no evidence of carcinogenicity in long-term, two- species rodent studies: the need for short-term test data. *Environ Mutagen* 1984;6:871-878.

170. Short RD, Johannsen FR, Levinskas GJ, Rodwell DE, Schardein JL. Teratology and multi-generation reproduction studies with maleic anhydride in rats. *Fundam Appl Toxicol* 1986;7:359-366.

171. Short RD, Johannsen FR, Ulrich CE. A 6-month multispecies inhalation study with maleic anhydride. *Fundam Appl Toxicol* 1988;10:517-524.

172. Sikora R, Harris KE, Kenamore B, Grammer LC. Immunoglobulin E antibody against environmental allergens in subjects with trimellitic anhydride-induced asthma. *J Occup Environ Med* 1999;41:190-194.

173. Smyth HF, Jr., Carpenter CP, Weil CS, Pozzani UC, Striegel JA, Nycum JS. Range-finding toxicity data: List VII. *Am Ind Hyg Assoc J* 1969;30:470-476.

174. Tarvainen K, Jolanki R, Estlander T, Tupasela O, Pfaffli P, Kanerva L. Immunologic contact urticaria due to airborne methylhexahydrophthalic and methyltetrahydrophthalic anhydrides. *Contact Dermatitis* 1995;32:204-209.

175. Taylor AJ, Venables KM, Durham SR, Graneek BJ, Topping MD. Acid anhydrides and asthma. *Int Arch Allergy Appl Immunol* 1987;82:435-439.

176. Topping MD, Venables KM, Luczynska CM, Howe W, Taylor AJ. Specificity of the human IgE response to inhaled acid anhydrides. *J Allergy Clin Immunol* 1986;77:834-842.

177. Turner ES, Pruzansky JJ, Patterson R, Zeiss CR, Roberts M. Detection of antibodies in human serum using trimellityl-erythrocytes: direct and indirect haemagglutination and haemolysis. *Clin Exp Immunol* 1980;39:470-476.

178. Ullmann F. *Ullmann's encyclopedia of industrial chemistry*. Weinheim: VCH Publishers, Inc., 1996.

179. United Nations, Economic commission for Europe. *Chemical Industry in 1998. Annual Review. Production and Trade Statistics 1995-1997*. New York: United Nations, 1998.

180. Vainiotalo S, Pfaffli P. Air impurities in the PVC plastics processing industry. *Ann Occup Hyg* 1990;34:585-590.

181. van Tongeren MJ, Barker RD, Gardiner K, Harris JM, Venables KM, Harrington JM, Newman Taylor AJ. Retrospective exposure assessment for a cohort study into respiratory effects of acid anhydrides. *Occup Environ Med* 1998;55:692-696.

182. van Tongeren MJ, Barker RD, Gardiner K, Harris JM, Venables KM, Taylor AJ, Harrington JM. Exposure to acid anhydrides in three resin and one cushioned flooring manufacturing plants. *Ann Occup Hyg* 1995;39:559-571.

183. Venables KM. Low molecular weight chemicals, hypersensitivity, and direct toxicity: the acid anhydrides. *Br J Ind Med* 1989;46:222-232.

184. Venables KM, Newman Taylor AJ. Exposure-response relationships in asthma caused by tetrachlorophthalic anhydride. *J Allergy Clin Immunol* 1990;85:55-58.

185. Venables KM, Topping MD, Howe W, Luczynska CM, Hawkins R, Taylor AJ. Interaction of smoking and atopy in producing specific IgE antibody against a hapten protein conjugate. *Br Med J (Clin Res Ed)* 1985;290:201-204.

186. Venables KM, Topping MD, Nunn AJ, Howe W, Newman Taylor AJ. Immunologic and functional consequences of chemical (tetrachlorophthalic anhydride)-induced asthma after four years of avoidance of exposure. *J Allergy Clin Immunol* 1987;80:212-218.

187. Vernot EH, MacEwen JD, Haun CC, Kinkead ER. Acute toxicity and skin corrosion data for some organic and inorganic compounds and aqueous solutions. *Toxicol Appl Pharmacol* 1977;42:417-423.

188. Ward MJ, Davies D. Asthma due to grinding epoxy resin cured with phthallic anhydride. *Clin Allergy* 1983;13:165-168.

189. Welinder H, Gustavsson C. Methyltetrahydrophthalic anhydride in air--sampling and analysis. *Ann Occup Hyg* 1992;36:189-197.

190. Welinder H, Nielsen J. Immunologic tests of specific antibodies to organic acid anhydrides. *Allergy* 1991;46:601-609.

191. Welinder H, Nielsen J, Bensryd I, Björk B, Strömberg U, Skerfving S. Decline in serum antibodies to methyltetrahydrophthalic anhydride after cessation of exposure. Implications for use as a biomarker. *Biomarkers* 1998;3:141-148.

192. Welinder H, Nielsen J, Gustavsson C, Bensryd I, Skerfving S. Specific antibodies to methyl-tetrahydrophthalic anhydride in exposed workers. *Clin Exp Allergy* 1990;20:639-645.

193. Welinder H, Nielsen J, Rylander L, Ståhlbom B. A prospective study of the relationship between exposure and specific antibodies in workers exposed to organic acid anhydrides. *Allergy* 2001;56:506-511.

194. Welinder H, Zhang X, Gustavsson C, Björk B, Skerfving S. Structure-activity relationships of organic acid anhydrides as antigens in an animal model. *Toxicology* 1995;103:127-136.

195. Welinder HE, Jönsson BA, Nielsen JE, Ottosson HE, Gustavsson CA. Exposure-response relationships in the formation of specific antibodies to hexahydrophthalic anhydride in exposed workers. *Scand J Work Environ Health* 1994;20:459-465.

196. Wernfors M, Nielsen J, Schutz A, Skerfving S. Phthalic anhydride-induced occupational asthma. *Int Arch Allergy Appl Immunol* 1986;79:77-82.

197. Winter C, Tullius E. The irritating effeets of maleic acid and of maleic anhydride upon the eyes of rabbits. *Am J Ophthalmol* 1950;33:387-388.

198. Yan ZQ, Hansson GK, Skoogh BE, Lötvall JO. Induction of nitric oxide synthase in a model of allergic occupational asthma. *Allergy* 1995;50:760-764.

199. Yokota K, Johyama Y, Yamaguchi K, Fujiki Y, Takeshita T, Morimoto K. Study on allergic rhinitis in workers exposed to methylterahydrophthalic anhydride. *Environ Health Prev Med* 1996;1:133-135.

200. Yokota K, Johyama Y, Yamaguchi K, Fujiki Y, Takeshita T, Morimoto K. Risk factors for sensitisation to methyltetrahydrophthalic anhydride. *Occup Environ Med* 1997;54:667-670.

201. Yokota K, Johyama Y, Yamaguchi K, Fujiki Y, Takeshita T, Morimoto K. Specific antibodies against methyltetrahydrophthalic anhydride and risk factors for sensitization in occupationally exposed subjects. *Scand J Work Environ Health* 1997;23:214-220.

202. Yokota K, Johyama Y, Yamaguchi K, Takeshita T, Morimoto K. Exposure-response relationships in rhinitis and conjunctivitis caused by methyltetrahydrophthalic anhydride. *Int Arch Occup Environ Health* 1999;72:14-18.

203. Yokota K, Takeshita T, Morimoto K. Prevention of occupational allergy caused by exposure to acid anhydrides. *Ind Health* 1999;37:281-288.

204. Yokota K, Yamaguchi K, Takeshita T, Morimoto K. The association between serum levels of Th cytokines and rhinoconjunctivitis caused by methyltetrahydrophthalic anhydride. *Allergy* 1998;53:803-807.

205. Yokota K, Yamaguchi K, Takeshita T, Morimoto K. The significance of specific IgG4 antibodies to methyltetrahydrophthalic anhydride in occupationally exposed subjects. *Clin Exp Allergy* 1998;28:694-701.

206. Young RP, Barker RD, Pile KD, Cookson WO, Taylor AJ. The association of HLA-DR3 with specific IgE to inhaled acid anhydrides. *Am J Respir Crit Care Med* 1995;151:219-221.

207. Zeiger E, Haworth S, Mortelmans K, Speck W. Mutagenicity testing of di(2-ethylhexyl)-phthalate and related chemicals in Salmonella. *Environ Mutagen* 1985;7:213-232.

208. Zeiss CR, Leach CL, Levitz D, Hatoum NS, Garvin PJ, Patterson R. Lung injury induced by short-term intermittent trimellitic anhydride (TMA) inhalation. *J Allergy Clin Immunol* 1989;84:219-223.

209. Zeiss CR, Leach CL, Smith LJ, Levitz D, Hatoum NS, Garvin PJ, Patterson R. A serial immunologic and histopathologic study of lung injury induced by trimellitic anhydride. *Am Rev Respir Dis* 1988;137:191-196.

210. Zeiss CR, Levitz D, Chacon R, Wolkonsky P, Patterson R, Pruzansky JJ. Quantitation and new antigenic determinant specificity of antibodies induced by inhalation of trimellitic anhydride in man. *Int Arch Allergy Appl Immunol* 1980;61:380-388.

211. Zeiss CR, Levitz D, Leach CL, Hatoum NS, Ratajczak HV, Chandler MJ, Roger JC, Garvin PJ. A model of immunologic lung injury induced by trimellitic anhydride inhalation: antibody response. *J Allergy Clin Immunol* 1987;79:59-63.

212. Zeiss CR, Mitchell JH, Van Peenen PF, Harris J, Levitz D. A twelve-year clinical and immunologic evaluation of workers involved in the manufacture of trimellitic anhydride (TMA). *Allergy Proc* 1990;11:71-77.

213. Zeiss CR, Mitchell JH, Van Peenen PF, Kavich D, Collins MJ, Grammer L, Shaughnessy M, Levitz D, Henderson J, Patterson R. A clinical and immunologic study of employees in a facility manufacturing trimellitic anhydride. *Allergy Proc* 1992;13:193-198.

214. Zeiss CR, Patterson R, Pruzansky JJ, Miller MM, Rosenberg M, Levitz D. Trimellitic anhydride-induced airway syndromes: clinical and immunologic studies. *J Allergy Clin Immunol* 1977;60:96-103.

215. Zeiss CR, Patterson R, Venables KM. Acid anhydrides. In: Bernstein IL, Chang-Yeung M, Malo J-L, Bernstein DI, eds. *Asthma in the workplace*. 2nd ed. New York, Basel: Marcel Dekker, Inc., 1999:479-500.

216. Zeiss CR, Wolkonsky P, Pruzansky JJ, Patterson R. Clinical and immunologic evaluation of trimellitic anhydride workers in multiple industrial settings. *J Allergy Clin Immunol* 1982;70:15-18.

217. Zhang X. *Relationship between chemical structure and airway sensitizing potential for organic acid anhydrides : an animal model*. Lund university, 1997 (doctoral thesis).

218. Zhang XD, Lötvall J, Arakawa H, Welinder H, Skerfving S. Relationship between IgG1 levels and airway responses in guinea pigs actively and passively sensitized to hexahydrophthalic anhydride. *Allergy* 1998;53:20-27.

219. Zhang XD, Lötvall J, Skerfving S, Welinder H. Antibody specificity to the chemical structures of organic acid anhydrides studied by in-vitro and in-vivo methods. *Toxicology* 1997;118:223-232.

220. Zhang XD, Welinder H, Jönsson BA, Skerfving S. Antibody responses of rats after immunization with organic acid anhydrides as a model of predictive testing. *Scand J Work Environ Health* 1998;24:220-227.

221. Zhao H, Zhang XD, Welinder H, Jonson B. Anaphylactic bronchoconstriction in immunized guinea pigs provoked by inhalation and intravenous administration of hexahydrophthalic anhydride and methyltetrahydrophthalic anhydride. *Allergy* 1997;52:18-26.

19. Databases used in the search for literature

In the literature search the following databases were used (June 2001):
NIOSHTIC
Medline
Toxline
Rtecs
Tomes
HSE-line
CISDOC

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Appendix

Occupational exposure limits for cyclic acid anhydrides in air.

Phthalic anhydride (TWA)

Country	ppm	μg/m^3		Comments	Year	Reference
Denmark		1 000			2002	(1)
Finland		200			2002	(2)
Germany		1 000	MAK	SEN	2003	(3)
Iceland	1	6 000		SEN	1999	(4)
The Netherlands		1 000			2002	(5)
		2 000	CL			
Norway		2 000		SEN	2003	(6)
Sweden		2 000		SEN	2000	(7)
		3 000	CL			
United States					2003	(8)
ACGIH	1	6 100		SEN		
NIOSH	1	6 000				
OSHA	2	12 000				
Great Britain		4 000	MEL	SEN	2002	(9)
		12 000	STEL			

Abbreviations: CL, ceiling; MAK, maximum workplace concentration; MEL, maximum exposure limit; SEN, sensitiser; STEL, short term exposure limit; TWA, time weighted average.

Trimellitic anhydride (TWA)

Country	ppm	μg/m^3		Comments	Year	Reference
Denmark		40			2002	(1)
Finland	0.005	40			2002	(2)
Germany		40	MAK	SEN	2003	(3)
Iceland	0.005	40	STEL		1999	(4)
The Netherlands		40	CL		2002	(5)
Norway	0.005	40		SEN	2003	(6)
Sweden		40		SEN	2000	(7)
		80	CL			
United States					2003	(8)
ACGIH	0.005	40	CL			
NIOSH	0.005	40				
OSHA	0.005					
Great Britain		40	MEL	SEN	2002	(9)
		120	STEL			

Abbreviations: CL, ceiling; MAK, maximum workplace concentration; MEL, maximum exposure limit; SEN, sensitiser; STEL, short term exposure limit; TWA, time weighted average.

Maleic anhydride (TWA).

Country	ppm	μg/m^3		Comments	Year	Reference
Denmark	0.1	400			2002	(1)
Finland		410			2002	(2)
		810	STEL			
Germany		410	MAK	SEN	2003	(3)
Iceland	0.1	400		SEN	1999	(4)
The Netherlands		400			2002	(5)
Norway	0.2	800		SEN	2003	(6)
Sweden	0.3	1 200		SEN	2000	(7)
United States						(8)
ACGIH	0.1	400		SEN	2003	
NIOSH	0.25	1 000				
OSHA	0.25					
Great Britain		1 000	MEL	SEN	2002	(9)
		3 000	STEL			

Abbreviations: CL, ceiling; MAK, maximum workplace concentration; MEL, maximum exposure limit; SEN, sensitiser; STEL, short term exposure limit; TWA, time weighted average.

In addition to the occupational exposure limits for phthalic anhydride, trimellitic anhydride and maleic anhydride presented in tables, the corresponding limits for two other cyclic acid anhydrides have been given in Finland in 2000: Methyltetra-hydrophthalic anhydride 170 μg/m^3 and Tetrachlorophthalic anhydride 200 μg/m^3, ceiling 400 μg/m^3 (4).

References

1. *Graensevaerdier for stoffer og materialer*. Køpenhavn: Arbejdstilsynet, 2002. www.at.dk/sw6796.asp

2. *HTP-arvot 2002*. Tampere: Sosiaali- ja terveysministeriö, 2002. www.ketsu.net/htp/2002.pdf

3. *BIA-Report 2/2003. Grenzwerteliste 2003*. HVBG. www.hvbg.de

4. *Reglur og leidbeiningar um menguarmörk og adgerdir til ad draga ur mengun a vinnustödum*. Reykjavik: Vinnueftirlit rikisins, 1999.

5. *Nationale MAC-Lijst 2002*. Den Haag: Sdu Uitgevers, 2002.

6. *Administrative normer for forurensninger i arbeidsatmosfaere*. Veiledning til arbeidsmiljoloven. Oslo: Direktoratet för arbeidstilsynet, 2003. (Bestillningsnr. 361)

7. *Hygieniska gränsvärden och åtgärder mot luftföroreningar*. Stockholm: Arbetarskyddsstyrelsen, 2000. ISBN 91-7930-357-9.

8. *Guide to occupational exposure values 2003*. ACGIH$^{®}$. www.acgih.org

9. *EH40/2002. Occupational exposure limits 2002*. HSE. www.hse.gov.uk