Social Europe

Recommendation from the Scientific Committee on Occupational Exposure Limits for phthalic anhydride

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8 hour TWA	:
STEL	:
Notation	: respiratory sensitizer skin sensitizer

Substance identification

Phthalic anhydride
Synonyms phthalic acid anhydride
1,2-benzenedicarboxylic acid anhydride
1,3-dioxophthalan,
1,3-phthalandione
1,3-isobenzofurandione

CAS No 85-44-9
Molecular formula $C_8H_4O_3$
MWt: 148.12

Physical and chemical properties

Conversion factors in air (25°C, 101.3 kPa) 1 ppm = 6.046 mg/m3
1 mg /m3 = 0.165 ppm

Description	White crystalline needles
Melting point	130.8°C
Boiling point	284°C (sublimes)
Vapour pressure (volatility)	<6.6 Pa at 20°C Vapour density (air=1) 5.1 3.4
Specific gravity	1.53
Density (water=1)	1.53
Solubility in water	0.62 g/100 ml
Solubility in organic solvents	Alcohol, ether
Partition coefficient (octanol/water)	log Pow: -0.62
Odour threshold	0.32 mg/m^3

1. Occurrence, production and use

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 (Venables 1989).

The annual world production of PA has been about 2 200 000 tonnes during the past decades, the European share being about 820 000 tonnes. The main producers in Europe are Belgium, the United Kingdom, the Russian Federation, Italy, and Germany (UN 1998).

Phthalic anhydride is produced by oxidation of o-xylene. The technical grade contains 99.9 % of PA and small amounts (0.03%) of maleic anhydride and 0.03% benzoic acid as impurities (Pfäffli et al 1991, Ullmann 1996). Phthalic anhydride is used in the manufacture of phthalate plasticizers, phthaleins, unsaturated polyester resins, alkyd resins, halogenated anydrides, and phthalocyanide dyes. It is also used in the preparation of benzoic acid and as a hardener in epoxy resins (NEG/DECOS 2004).

Occupational exposure

Since the introduction of phthalic anhydride (PA) several new derivatives of cyclic acid anhydrides have come 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 (NEG/DECOS 2004).

In studies from the 1980´s, the highest concentrations have generally occurred in the production of PA and unsaturated polyester resins in flaking, sacking, loading of reactors and charging with PA in solid form. Especially high concentrations (320-17 400 µg/m3) were measured during malfunction and in loading of reactors (Nielsen et al 1988, Pfäffli 1986). More recent studies from three plants producing alkyd resins reported much lower concentrations (AM 0.5-138 ug/m3) in the production of alkyd resins (van Tongeren et al 1995). Still, charging operations ranged up 1 860 µg/m3 (van Tongeren et al 1995). The PA concentrations during polyvinyl chloride (PVC) processing were low, ranging from less than 0.02 to 5 µg/m3 (Vainiotalo & Pfäffli 1990).

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 (Pfäffli 1986). Cyclic anhydrides have also been detected in welding fumes from painted steel (Henricks-Eckerman et al 1990, Keskinen et al 2000).

2. Health significance

Toxicokinetics

All cyclic anhydrides react with water, especially if heated, and the corresponding acids are formed (Lewis 1996).

There are no data on absorption via the gastrointestinal system. The dermal absorption is minute. For the rabbit, the dermal LD50 was determined to be 10.000 mg/kg body weight (BioFax 1970).

Acid anhydrides are used to change the properties of proteins to separate them from their matrix (Palacian et al 1990). The anhydride group reacts readily with amino acids. This explains their conjugation with human serum albumin (HSA), which takes place in the hapten formation of acid anhydrides (Taylor et al 1987, Zeiss et al 1977).

Pfäffli (1986) 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 µg/m3, range 30-330 µg/m3) 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 µg/m3, SD 130µg/m3), the pre-shift phthalic acid excretion was 1.02 (SD 0.25) µmol/mmol creatinine indicating an accumulation of phthalic acid in urine. At high exposure, 10 500 µg/m3, the pre-shift urinary concentration increased to 4.8 µmol/mmol creatinine, which was about 14 times higher than in workers with low exposure. No conjugation of phthalic acid to glucuronide was observed (Pfäffli 1986).

The half-time of phthalic acid in urine of PA-exposed workers was shown to be about 14 hours (Pfäffli 1986). The halftime for the dicarboxylic acid of PA in urine was 14 hours.

In cross-sectional studies the proportion of persons with immunoglobulin IgG specific for PA increased as exposure increased (Nielsen et al 1988, Welinder et al 1990, Welinder et al 1994). However, 50% or more of the subjects were negative even in the groups with the highest exposure intensity. Thus, the value of IgG as a biomarker of exposure is limited.

Measurements and analysis of workplace exposure

Sensitive methods are available to measure air levels of exposure to phthalic anhydride and the corresponding dicarboxylic acid to PA. Pfäffli sampled PA from air with Tenax polymer tubes and analysed PA by GC utilising a 63Ni-ECD. The limit of detection was 0.4 µg/m3 (0.00007 ppm) with an air sample of 12 1(Pfäffli 1986, Pfäffli 1994). PA can also be analysed as the corresponding phthalic acid by reversed phase high performance liquid chromatography (HPLC), as described by Nielsen et al. (1988).

Sensitive methods exist for the measurement of the dicarboxylic acids of several of the cyclic anhydrides, including PA, in urine. The detection limit for phthalic acid was 15 ng/ml (Pfäffli et al 1989). Phthalic acid in urine correlates to PA in air. At an exposure level corresponding to 30% of the hygienic reference value at the time of 6000 µg/m3, a body-burden was accumulated which was not eliminated over night (Pfäffli 1986).

Mechanisms of toxicity

Irritation

PA is irritant to the skin, eys and the mucous membranes of the respiratory tract. The irritative mechanism depends on the hydrolysis of PA to phthalic acid. (Frans & Pahulycz 1993 , Gad et al 1986).

Allergic contact dermatitis (Type IV)

In animal studies PA has been classified as a moderate sensitizer causing allergic contact dermatitis of type IV allergy (Gad 1988). This receives support by the paucity of reports on PA-induced allergic contact dermatitis.

Contact urticaria (Type I)

IgE-mediated contact urticaria due to cyclic acid anhydrides is more common than contact dermatitis (NEG /DECOS2004).

Respiratory sensitization

Allergic asthma, often preceded by rhino-conjunctivitis, is a well documented disease of workers exposed to cyclic acid anhydrides including PA. In case reports and industrial surveys, IgE-mediated sensitization has been verified by positive reactions in skin prick tests with PA-HSA conjugates, and by the demonstration of specific IgE to PA. In exposed workers, bronchial hyperresponsiveness, a characteristic feature of asthma, has been correlated to the specific sensitization (Barker et al 2000). Immediate, dual, or late bronchial reactions have been found in inhalation challenge tests with PA, (Baur et al 1995, Durham et al 1987, Wernfors et al 1986).

The formation of protein adducts in vivo is believed to be the first step in the sensitization process. This has been shown when total protein and albumin adducts of HHPA and MHHPA were measured in the plasma of exposed workers (Rosqvist et al 2000).

Formation of anhydride-specific IgE and IgG antibodies has been demonstrated also in experimental animal studies (Arts et al 1998, Zhang et al 1998). An obstructive bronchial reaction has followed the challenge tests of sensitized animals (Arts et al 1998, Sarlo et al 1994).

There are some findings of mediator release in acid anhydride sensitivity. Basophilic leukocytes when challenged with a PA-HSA conjugate, released 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 an IgE-mediated reaction (Flaherty et al 1988).

Experimental animal and in vitro studies

Acute toxicity

Inhalation

A one-hour inhalation exposure to phthalic anhydride at a concentration of 210 mg/m3 caused lacrimation in the rat, but no other symptoms or deaths (BioFax 1970).

In a study on pulmonary sensory irritation due to PA dust, rats were exposed (head only) for 10 minutes to a concentration of 574 mg/m3, the maximum technically possible. This exposure did not cause effects on respiratory function; thus this study did not indicate a sensory irritation from the dust. Likewise, another study with phthalic anhydride vapour carried out according to the same test protocol indicated no sensory irritation after exposure to the highest concentration (11 mg/m3 (CMA 1995)

Ingestion

Table 1 presents data on the lethal dose for 50% of the exposed animals at single administration (LD50) of phthalic anhydride.

Table 1: Acute lethal dose for phthalic anhydride

Species	Route of administration	LD_{50} (mg/kg bw)	References
Cat	Oral	800	NIOSH 2001
Rat	Oral	1530	NIOSH 2001
Mouse	Oral	1500	NIOSH 2001
Mouse	Intraperitoneal	75.5	Fabro et al 1982

The LD_{50} for rat was given at approximately 2000 mg/kg body weight by HSE (1996).

Subacute, subchronic and chronic toxicity

In a four-week study, PA was administered to albino rats at 250, 1000 or 3800 mg/kg feed corresponding to 20.7, 82.2, 319.6 mg/kg body weight, respectively. At autopsy, no striking macroscopic findings were noted; body weight gain and weight of examined organs were normal (liver, kidney, adrenal glands, testes) (BioFax 1970).

Local effects on skin and mucous membranes

A PA solution (50%) in oil did not irritate rabbit ears after 20 hours of exposure

(DFG 1986/1987). 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 (Potokar et al 1985). PA did not produce irritation to the skin of rabbits when exposed for 24 hours at 500 mg/animal (Bomhard et al 1996). In another study 500 mg/animal for 24 hours having the test substance moistened, slight irritation was reported (BioFax 1970).

One drop of PA (5%) in polyethylene glycol 400 was slightly irritating to rabbit eyes, while a 0.5% solution was not irritating (DFG 1986/87) . 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 (Gad et al 1986). Introduction of PA into the eye at 50mg/animal caused irritation and a temporary corneal clouding in rabbits (Bomhard et al 1996). In a study with a follow-up period of only 3 days and an application of 100 mg/animal, the pronounced effects (71-81/110) were not reversible (BioFax 1970).

Table 2. Irritative effects of acid anhydrides on different animal species.

Species	Route of administration	Exposure data	Effect	Reference
Rabbit	Eye application	50 mg	Moderate irritation	NIOSH 2001
Rabbit	Eye application	50 mg	Irritation, corneal temporary clouding	Bomhard et 1996
Rabbit	Dermal (patch)	500 mg (1or4 h)	No skin irritation	Potokar et al 1985
Rabbit	Dermal	500 mg (test substance)	Slight irritation	BioFax 1970

Sensitizing effects

Immunization of animal species as verified with specific IgE and IgG antibodies, followed cutaneous administration or single intradermal injection with free or conjugated PA (Hakanaka et al 1997, Zhang et al 1998). Repeated short-term exposures (subcutaneous or inhalation) to PA (or the corresponding conjugate) induced specific IgG antibody formation in a dose-response manner in guinea pigs. In challenges after sensitization, more positive tests were seen when a higher dose was used (Sarlo et al 1994) (Table 3).

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 sensitizer (Gad et al 1986). In the guinea pig maximization test, PA was found to have sensitizing effects. The test was performed using intradermal induction 0.1 %, dermal induction 25%, dermal provocation 10 %and as vehicle acetone/polyethylene glycol 400 (Basketter and Scholes 1992). In other studies investigating the patterns in cytokine production following topical sensitization, PA was not found to be a contact allergen (Dearman & Kimber 1992, Dearman et al 2000).

PA has had sensitizing effects in the local lymph node assay at all three used induction concentrations, 2.5, 5 or 10% in acetone/olive oil. (Ashby et al 1995, Basketter and Scholes 1992, Kimber et al 1989). PA was also positive in a local lymph node test at 25% in acetone/oil (Vandebriel et al 2001).

Respiratory sensitization

Sensitization 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 routes of administration.

Guinea pigs were sensitized by inhalation of PA dust at 500, 1 000, 5 000 µg/m3, 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/m3) 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 (Sarlo et al 1994). A single intradermal injection of phthalic anhydride (0.3 M) to guinea pigs was followed by the production of specific IgG (Welinder et al 1995). After intradermal injection of hexahydrophthalic anhydride to guinea pigs, the provocation with a phthalic anhydride conjugate caused reactions in the respiratory passages (Zhang et al 1997).

A single intradermal injection of a 0.3% PA solution in acetone/oil to guinea pigs did not cause any pulmonary effect on inhalation provocation (44 mg/m3) at 22 days. Another test in guinea pigs comprised intradermal injection of 0.03, 0.1 or 0.3 % PA in corn oil with consequent inhalation provocation with 11-29 mg/m3 in argon or 9-48 mg/m3 in dry air. Intradermal injection of 0.5 % solution and provocation with 11-29 mg/m3 in argon resulted in respiratory effects. At the lower concentrations, 0.03 and 0.1 % local irritant effects were seen in both test and control animals (Blaikie et al 1995).

Three weeks after a 5-day exposure to 0.5 mg/m3 for 6 hours/day, the provocation treatment with 0.5 mg/m3 also caused an increase in haemorrhagic foci in the lungs of rats, which was assessed to be a sign of airway sensitization.

In a Japanese study, rabbits were sensitized subcutaneously to a PA- RSA (rat serum albumin) conjugate. 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 (Hatanaka et al 1997).

When monkeys were exposed parenterally to PA-MSA (monkey serum albumin), PA dissolved in ethanol saline, MSA, or ethanol-saline alone, sensitization was observed only with PA-MSA. The presence of new antigenic determinants formed by PA on protein carriers was essential for the parenteral sensitization (Biagini et al 1988).

Table 3 Sensitizing effects of PA in animals in short-term exposure studies.

PA	Route of administration	Exposure data	Effects	Reference
Guinea pig	inhalation	500, 1000, 5000 µg/m3 PA dust 3 h/day for 5 days, challenged with PA-GPSA 2000 µg/m3 or PA dust 5000 µg/m3	IgG abs in lowest exposure category greater than in air exposure (p 0.05. Dose-response in IgG abs (p 0.0019. Haemorrhagic lung foci in highest exposure after PA dust challenge	Sarlo et al 1994
Rabbit	subcutaneous	PA-RSA 0.25 ml weekly/12 weeks	high titre IgG to PA-RSA and PA-HSA, cross-reactivity with HHPA-, MHHPA-, MTHPA-HSA conjugates	Hatanaka et al 199

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-increase max at 14 days. IgE-antihapten antibodies in PCA test. IgG_{2b} antihapten antibody production	Dearman & Kimber 1992
Rat, brown	Intradermal	0.1 ml 0.2 M PA	Specific IgE and Specific IgG anti bodies	Zhang et al 1998

Effects in humans

The most common PA-induced allergic diseases are rhinoconjunctivitis and asthma, both immediate-type IgE-mediated allergies. Also late-type respiratory symptoms with specific IgG antibodies have been described. Less frequent consequences are contact eczema, contact urticaria, allergic laryngitis, and allergic alveolitis (HSE 1996, ACGIH 2000, DFG 2001, NEG/DECOS 2004).

Irritation

Conjunctival, nasal, and bronchial irritation is a common immediate feature following exposure to acid anhydrides. The irritative symptoms (itching, lacrimation, sneezing, rhinorrhoea, cough, and dyspnoea) begin immediately at exposure to high concentrations of dust or vapours (Baader 1955, Nielsen et al 1988). On mucous membranes and on sweating skin, PA is hydrated to phthalic acid causing irritation, reddening, corneal damage, caustic dermatitis, and burns (Malten & Zielhuis 1964).

In early reports, irritation of the mucous membranes was a common immediate response in workers highly exposed to acid anhydrides in powder form (Baader 1955, Menschick 1955, Nielsen et al 1988). The human nasal irritation threshold for PA has been reported to be 30 000 µg/m3. However, exposure duration, generation of particles and particle sizes were not given (Ruth 1986).

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 (Gautrin et al. 1999). 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 non-specific bronchial hyperreactivity was verified, which resolved after about 3.5 years (Frans & Pahulycz 1993).

Sensitization

Sensitization of the skin

Respiratory diseases include occupational allergic rhinoconjunctivitis and occupational asthma. Urticaria and allergic rhinoconjunctivitis often precede asthma. In industrial surveys the prevalence of occupational asthma due to different anhydrides has varied between 8-18% in those exposed to PA (NEG/DECOS 2004).

Allergic dermatitis due to cyclic acid anhydrides appears in general to be rare (HSE 1996). Two cases of urticaria has been described following air-borne exposure to MHHP, both of which showed a positive prick test also to a PA-conjugate and they had specific IgE-

antibody in the serum (Tarvainen et al 1995). 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 (Motolese et al 1993).

Sentization of the airways

Cases of occupational asthma and rhinitis have been reported from various work environments associated with exposure to PA. Typical environments include PA production (Moscato et al 1986, Nordman et al. 1986), production of alkyd or unsaturated polyester resins (Barker et al 1998, Nielsen et al 1988, Wernfors et al 1986), paint and varnish production (Fawcett et al 1977, Kern 1939, Gervais et al 1972), plastic grinding (Ward and Davies 1983), tyre and rubber manufacturing (Chester et al 1977). Some effects of PA in occupationally workers have been compiled in table 4.

Acid anhydrides cause an IgE- mediated, immediate-type asthma and rhinitis (HSE 1996, NEG/DECOS 2004, DFG 2001). The first case of PA-induced asthma reported by Kern in 1939 was already demonstrated to have an immunological mechanism; the scratch test with PA in crystalline form and diluted 1:1 000 in alcohol gave positive reactions whereas tests with control patients were negative. The passive transfer test was also positive (Kern 1939).

Table 4: Effects and antibody formation in workers occupationally exposed to PA

Exposure level (µg/m3	No exposed	Exposure duration months	Effects	Specific IgE-antibody 1)	Specific IgG-antibody 2)	Reference
<300-13000	118	2 - 40 yr	Rhinitis 28 (24%) Asthma 21 (18%)			Wernfors et al 1986
6600 (1500-17400) (TWA 400)	35	0 - 43 yr	Conjunctivitis 16 (46%) Rhinitis 14 (40%) Rhino-conjunctivitis 6 (17%) Asthma 5 (14%)	0.9 (0.5-28)	2.5 (0.7-7.1)	Nielsen et al 1988
<100 3) (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)	Nielsen et al 1988
0	22		No symptoms	1.0 (0.4-2.2)	1.1 (0.5-3.2)	
0.4-2500 ug/m3	401		Work-related respi-ratory symptoms in 34 (8.8%),	prick-test with PA-HSA conjugate positive in 12 (3.2%)	1.1 (0.5-3.2)	Barker et al 1998

1) RAST ratio, 2) ELISA ratio, 3) detection limit of the assay 0.1 mg/m3

Specific IgE-antibody in the serum of patients with asthma due to PA has been reported consistently (e.g. Maccia et al 1976, Nielsen et al 1988, Topping et al 1986, Nordman et al 1988, Welinder et al 2001). Inhibition studies and passive transfer studies have supported the specificity of IgE antibodies (Welinder & Nielsen 1991).

Immediate-type skin tests with phthalic anhydride-HSA conjugates have correlated well with the finding of specific IgE in serum (Baur & Czuppon 1995, Welinder & Nielsen 1991, Welinder et al 2001).

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 (Bernstein et al 1982,). 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 sensitized to TCPA and TMA, the antibody combines with the anhydride and the adjacent portion of the HSA molecule, whereas in patients sensitized to PA, the antibody is specific to the hapten (Topping et al 1986). TMA is claimed to form unique antigenic determinants that do not bind significantly with antibodies formed by sensitization to PA. This may explain the insignificant cross-reactivity with TMA and PA in inhibition studies (Bernstein et al 1982, Topping et al 1986, Zeiss et al 1999). PA-exposed subjects show a lower degree of cross-reactivity with other anhydrides than do other acid anhydrides (Welinder & Nielsen 1991).

Studies on dose-response relationships are scarce (table 4). The most helpful data come from a Swedish study carried out in two polyester resins plants, in which 60 workers exposed to PA for on an average of 12 years were surveyed (Nielsen et al 1988). The group was divided into a high exposure group of 35 and a low exposure group of 25 workers. The high exposure group had been exposed as reactor loaders to mean concentration of about 6.6 mg/m3 (1.5 - 17.4 mg/m^3) during loading, which lasted for about 30 minutes daily. Otherwise PA concentrations were below the detection limit of 0.1 mg/m3. An 8-hour TWA was calculated for the high exposure group at 400 ug/m3. They were also exposed to maleic, trimellitic and isophtalic anhydrides, but to a "much lower amount". The low exposure group had been exposed to a TWA<100 µg/m3. There was a reference group of 22 food processors. In the high exposure group the prevalence of conjunctivitis was 46%, rhinitis 40% and asthma 14%. The corresponding prevalences for the low exposure group were 20% of conjunctivitis, 20% rhinitis, and 0% asthma. Similar conditions were not found among references.

There was no association between specific IgE antibodies and PA exposure (table 4). Specific IgG-levels were at a group level higher in the high exposed group than in the low exposed group. Five workers with asthma had also higher IgG-levels than non-asthmatics. IgG-levels were not uniformly increased among asthmatics and IgG-levels were also increased in some non-asthmatics. The IgG4 levels were increased in three of the five asthmatics and in one worker with rhinitis. Nielsen et al (1988) concluded that specific IgG probably reflects exposure, whereas IgG4 subclass antibody seemed to correlate with symptoms and thus, may be a pathogenetic factor in asthma. Considering the rather short daily exposure (about 30 minutes) to high levels of PA during loading and a fairly low 8-hour TWA in the high exposure group, the authors suggested that symptoms probably were due to peak exposures. They also found it reasonable to suggest a ceiling value that should be "well below 6 mg/m3", the Swedish limit value at that time (Nielsen et al 1988).

The role of IgG-antibody subclasses in PA-induced respiratory allergy is not fully evaluated. Results similar to those by Nielsen et al (1988) were reported in a study carried out in a PA production plant with a work force of 70 exposed workers (Nordman et al 1988). The workers had been exposed to TWA levels ranging 0.03 - 10.5 mg/m3 and some of them may have been exposed to minute amounts of maleic anhydride (Pfäffli 1986). In nine of the workers rhinitis symptoms had started after about six months of exposure being followed by breathlessness about one year later. A clinical evaluation of 26 workers with

respiratory work-related symptoms was performed including bronchial provocation tests with either PA flakes or PA fumes at 0.35-2.0 ppm (2.1-12.1 mg/m3), simulating the work exposure conditions. The provocation test resulted in 11 cases of occupational asthma; 8 workers reacted with a positive nasal reaction consistent with their symptoms at work. The bronchial reactions were immediate (5), late (3) and dual (3). Six out of 11 asthmatics had at some point of time been exposed to high concentrations working at the bagging machine. All five asthmatics with positive skin tests with PA-HSA or RAST displayed immediate bronchial reactions and were considered IgE-mediated. Of the 8 nasal reactions only one was skin test positive, none was RAST positive. Out of 15 workers with increased IgG4 levels only one was symptomless. Thus, the IgG4 concentrations correlated with positive bronchial challenge tests as well as with work-related symptoms, indicating a possible mechanistic role of IgG4, similarly to the studies by Nielsen et al (1988, 1991).

Wernfors et al. studied 118 workers in four plants producing alkyd or unsaturated polyester resins. Forty-eight were current and 70 former employees. The PA dust concentrations during loading of reactors and in the handling of bags were high, up to 13 000 µg/m3. The fraction of respirable dust was about 40%. The authors found 28 (24%) persons with work-related rhinitis and 21 (18%) with asthma. Symptoms had started after at least one month of exposure. 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 two asthmatics. The skin positive patients were also challenge tested. The bronchial provocation tests with PA powder (6 000 µg/m3 for 5 minutes) caused a dual asthmatic reaction in one patient, whereas the test with was negative. The other patient experienced a dual reaction when challenged with the 500 µg/m3 of PA (Wernfors et al 1986).

A British historical cohort study has been reported. It consists of 506 workers exposed to PA for more than one month since the beginning of 1960 in four plants. Three factories manufacturing resins used principally PA, but also MA and TMA. 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 (van Tongeren et al 1998). A questionnaire on employment history, respiratory symptoms and smoking habits was completed by 401 (79%) workers. Skin prick tests with PA-HSA conjugates were positive in 12 (3.2%). Thirty-four (8.8%) had respiratory symptoms related to PA exposure. Positive skin tests correlated with work-related respiratory symptoms. Exposure to PA or MA was found to be uncommon as a cause of sensitization at the current low exposure levels measured in 1992 (0,4 - 2500 µg/m^3) (van Tongeren et al 1995; Barker et al 1998).

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 (Piirilä et al. 1997).

Predisposing factors

Smoking has been reported to interact with atopy in the production of IgE-antibodies against TCPA (Venables et al 1985). This effect of smoking has not been demonstrated in PA-exposed workers (Nielsen et al 1988).

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 sensitization. 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 cases and referents were atopic and smokers, the other risk factors for sensitization. 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 (Young et al 1995).

Reproductive and developmental studies

Fabro et al.(1982) studied the teratogenicity of PA 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 (Fabro et al 1982). 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 (Korhonen et al 1983)..

There are no data on the developmental effects of phthalic anhydride on human reproduction.

Mutagenicity and genotoxicity

There are no data showing mutagenic or genotoxic effects of pthalic anhydride in humans (HSE 1996, DFG 2001).

No mutagenic activity has been found with PA in Salmonella typhimurium in Ames test (Zeiger et al 1985). In a micronucleus test in F344 rats, PA did not indicate mutagenic effect (Heddle et al 1991). No effect of PA was found on chromosomal aberrations neither in cells derived from Chinese hamster ovary cells nor in rat liver cells in vitro (Galloway et al 1987, Phillips et al 1986). PA did not induce sister chromatid exchanges in Chinese hamster ovary cells (Galloway et al 1987). Using a higher and cytotoxic PA concentrations of 6, 8 and 10 mM in CHO cells, an 18.5% increase in chromosome aberrations was seen at the highest concentration. The authors considered the positivity to be false (Hilliard et al 1998).

Carcinogenicity

Long-term feeding studies on rat and mouse have not disclosed any evidence of carcinogenic effects of phthalic anhydride (HSE 1996, DFG 2001, Haseman et al 1987,Kluwe 1986, Kluwe et al 1982, Shelby & Stasiewicz 1984). There was no effect of PA in cell transformation tests performed in embryo cells of Syrian hamsters (LeBoeuf et al 1996). Neither did a transformations test with A-31-1-13 BALB/c-T-3T3 cells show any effect (Matthews et al 1993).

An in vivo study with male F344 rats, 15000 mg of PA/kg food was administered orally for 1 and 2 weeks. The formation of 8-hydaroxydeoxyguanosine in the DNA of liver and kidney. There were no differences between rats given PA and controls (Takagi et al 1990).

In a study on the dysregulation of ornithine decarboxylase as an early component in the multistage carcinogenesis, PA at a dose of 135 uM was tested in an in vitro test model using embryo cells of Syrian hamsters. PA did not exhibit any significant effects (Dhalluin et al. 1997, 1998).

In a case-control study, lung cancer mortality 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, also exposure to potential confounders, phthalates and soot (Riboli et al 1983).

Recommendation

Phthalic anhydride (PA) causes irritation and sensitization of the eyes and the respiratory tract. OA induces allergic rhinoconjuctivitis and asthma. From a health-based point of view, the allergic respiratory effects, being persistent, are the most severe effects of PA. it is not always possible to separate irritant and allergic effects. IgE-mediated asthma and rhinitis has been proven, but other unknown mechanisms may be involved. Experimental animal studies have demonstrated a weak skin sensitizing effect and skin sensitization has been reported in humans.

Human data on dose-response is poor. Based on the available scientific data, it is not possible to identify a NOAEL, nor a LOAEL for PA. Among workers exposed to 8-hour TWA levels of PA below 0.1 mg/m3 (0.1 being the detection limit of the PA assay) rhinitis, conjunctivitis and rhinoconjunctivitis occurred in a substantial proportion of exposed, whereas no cases of asthma were found. Whether the symptoms were irritant or allergic is uncertain (Nielsen et al 1988). Available experimental animal data are not of any further help in the assessment of a NOAEL or LOAEL.

Peak exposures are likely to be important inducers of sensitization. The recommendation of a STEL would, therefore be advisable, but a scientifically based value is impossible to assess based on available data.

Studies available do not indicate genotoxic, mutagenic or carcinogenic effects of PA

Data do not indicate significant absorption through the skin.

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Annex

ANALYTICAL INFORMATION ON LIMIT OF DETECTION FOR PHTHALIC ANHYDRIDE IN AIR AND IN URINE

AIR:

The analytical techniques used to determine this substance are HPLC-UV and GC-ECD.

For determining the workplace exposure to phthalic anhydride in air, Pfaeffli used a Tenax tube connected downstream in series with a membrane filter for collecting any vapor that had penetrated the filter. He desorbed the filter and the adsorbent with methyl t-butyl ether and analyzed directly for the anhydride with GC/ECD to eliminate the interference from phthalic acid present during sampling. But there is a possibility of collecting anhydride being partially hydrolyzed to phthalic acid before the analysis

OSHA has been collecting phthalic anhydride in isopropanol impingers and analyzing the resulting half ester by HPLC. This not only eliminates the interference from the phthalic acid originally present in the air, but also prevents the loss of anhydride through hydrolysis after it has been collected.

The following table summarises the limit of detection (LOD) of the methods available.

METHOD	YEAR OF PUBLICATION	ANALYTICAL DATA	LOD	REMARKS	COMPLIANCE WITH OEL
OSHA 90 HPLC-UV	1991	Recommended air volume:75 L Flow rate: 1 l/min Reliable quantitation limit: 0,008 ppm	0,005 ppm per sample	validate d	YES
Pfäffli Gas Chromatography	1986	Recommended air volume: 12 l Flow rate: 0,2 l/min	0,4µg/m^3	(?)	YES

Conclusion

An 8h-TWA of 1 ppm (6.05 mg/m3) for phthalic anhydride can be measured without difficulties.

URINE:

Electron capture gas chromatography has been used for selective and sensitive determination of phthalates in biological samples. Phtalic anhydride also shows a high electron capture response. Phthalic anhydride is converted to phthalic acid in the presence of water. A similar reaction may be envisaged in the living organism, where, after phthalic anhydride exposure, the excretion of phthalic acid is observed. Phthalic anhydride is excreted mainly as free acid and can be determined in urine at low concentrations by gas chromatography with ^{63}Ni-electron capture detection. Urinary concentrations in subjects exposed to atmospheric phthalic anhydride, show good correlations with the atmospheric concentration. The detection limit for urine samples (10 ml) was 0.05 µmol/l.

No measurement difficulties are foreseen to measure the BLV proposed at the end-of-shift.