FOREWORD INTRODUCTION

PHTHALIC ANHYDRIDE

CAS N°: 85-44-9

SIDS Initial Assessment Report

For

SIAM 20

Paris, France, 19–22 April 2005

1. Chemical Name:	Phthalic anhydride
2. CAS Number:	85-44-9
3. Sponsor Country:	Germany Contact Point: BMU (Bundesministerium fuer Umwelt, Naturschutz und Reaktorsicherheit) Contact person: Prof. Dr. Ulrich Schlottmann Postfach 12 06 29 D- 53048 Bonn
4. Shared Partnership with:	Atofina, France; BASF AG, Germany; Exxon Chemical Europe Inc., Belgium; LONZA AG, Switzerland; Perstorp SpA,Div. Polyols, Italy
5. Roles/Responsibilities of the Partners:	-
• Name of industry sponsor /consortium	Bayer AG, Germany Contact person: Dr. Burkhardt Stock D-51368 Leverkusen Building 9115
• Process used	see next page
6. Sponsorship History	
• How was the chemical or category brought into the OECD HPV Chemicals Programme?	by ICCA-Initiative
7. Review Process Prior to the SIAM:	last literature search (update): 14 November 2004 (Human Health): databases medline, toxline; search profile CAS-No. and special search terms 12 November 2004 (Ecotoxicology): databases CA, biosis; search profile CAS-No. and special search terms OECD/ICCA
8. Quality check process:	IUCLID was used as a basis for the SIDS dossier. All data were checked and validated by BUA. A final evaluation of the human health part has been performed by the Federal Institute for Risk Assessment (BfR) and of the ecotoxicological part by the Federal Environment Agency (UBA).
9. Date of Submission:	Deadline for circulation: 21 January 2005
10. Date of last Update:	Last literature search: IUCLID Chapters 1-4: 2004-02-03 Chapter 5: 2004-01-22

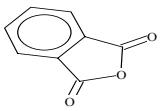
11. Comments: -

OECD/ICCA - The BUA* Peer Review Process

Qualified BUA personnel (toxicologists, ecotoxicologists) perform a quality control on the full SIDS dossier submitted by industry. This quality control process follows internal BUA guidelines/instructions for the OECD/ICCA peer review process and includes:
– a full (or update) literature search to verify completeness of data provided by industry in the IUCLID/HEDSET
– Review of data and assessment of the quality of data
– Review of data evaluation
– Check of adequacy of selection process for key studies for OECD endpoints, and, where relevant, for non-OECD endpoints by checking original reports/publications
– Review of key study description according robust summaries requirements; completeness and correctness is checked against original reports/publications (if original reports are missing: reliability (4), i.e. reliability not assignable)
– Review of validity of structure-activity relationships
– Review of full SIDS dossier (including SIAR, SIAP and proposal for conclusion and recommendation for further work)
– In case of data gaps, review of testing plan or rationale for not testing.

* BUA (GDCh-Beratergremium für Altstoffe): Advisory Committee on Existing Chemicals of the Association of German Chemists (GDCh)

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	85-44-9
Chemical Name	Phthalic anhydride
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

On contact with water, phthalic anhydride is rapidly hydrolyzed to phthalic acid. Unconjugated phthalic acid was found in the urine of humans exposed to phthalic anhydride by the inhalation route, demonstrating systemic absorption and elimination via the urine and the existence of phthalic acid as a hydrolysis product *in vivo*.

The oral LD_{50} in rats was 1530 mg/kg bw. Clinical signs at doses equal or higher than 500 mg/kg bw included sedation, imbalance, and bloodshot eyes. There were no reliable animal acute toxicity studies available for the inhalation and dermal routes of exposure.

In poorly documented human case reports, which provide no reliable information on exposure levels, headache, dizziness, nausea, epigastric burning and a feeling of suffocation were described after acute occupational exposure to phthalic anhydride dust or vapor.

In rabbits, phthalic anhydride was slightly irritating to the skin (OECD TG 404), and irritating to the eyes. In humans, effects on the eye after occupational exposure are described (including conjunctivitis, lacrimation, corneal ulceration, necrosis, and photophobia). For humans, phthalic anhydride in the form of vapor, fumes, or dust is a primary irritant to mucous membranes and the upper respiratory tract. Initial exposure produces coughing, sneezing, burning sensations in the nose and throat, and increased mucous secretion. Repeated or continued exposures may result in general inflammation of the respiratory tract, nasal ulceration and bleeding, atrophy of the mucous membranes (reversible), loss of smell, hoarseness, bronchitis, urticaria, and symptoms of allergic hypersensitivity.

Phthalic anhydride demonstrated skin sensitizing properties in animals, with positive results being observed in guinea pig tests according to OECD TG 406 and in local lymph node assays similar to OECD TG 429. Evidence that phthalic anhydride has respiratory sensitization potential has been demonstrated in an experimental guinea pig model. In humans, there are a number of reports providing information on the respiratory sensitization potential of phthalic anhydride after occupational exposure. Workers were reported to suffer from work-related rhinitis, chronic productive bronchitis, and work-associated asthma. Phthalic anhydride sensitization is generally associated with either an asthma-rhinitis-conjunctivitis syndrome or with a delayed reaction and influenza-like symptoms and with increased IgG and/or phthalic anhydride specific IgE levels in the blood. Reports on skin reactions in humans are rare.

Phthalic anhydride has been shown to have low repeated dose toxicity by the oral route in rats. The evidence of toxicity in a chronic rat study is limited to adverse effects on body-weight gain at the dose level of 1000 mg/kg bw/day. The NOAEL was at 500 mg/kg bw/day. It is noted that no hematology and clinical biochemistry examinations were performed in this study. A NOAEL could not be established in a chronic feeding study in mice because of pathological effects seen down to the lowest tested dose level (LOAELs: 12 019 ppm level in female mice = approximately 1717 mg/kg bw/day, and 16 346 ppm in male mice = approximately 2340 mg/kg bw/day; increased incidences of lung and kidney lymphocytosis in the males and females, and dose-related adrenal atrophy and mineralization of the thalamus in males. The LOAELs are time-weighted averages because a dose reduction in males from 25 000 to 12 500 ppm (= approximately 1785 mg/kg bw/day) and for females from 12 500 to 6250 ppm

(= approximately 890 mg/kg bw/day) was necessary after 32 weeks of exposure due to reduced weight gains). There were no valid repeated dose studies available using the dermal or respiratory routes of exposure.

Phthalic anhydride was not mutagenic in the Ames test with and without metabolic activation (OECD TG 471). Chromosomal aberrations were induced in mammalian cells *in vitro* at the highest phthalic anhydride concentrations (10 mM) only in the absence of S9 mix with concomitant marked cytotoxicity and compound precipitate. *In vivo* studies are not available. Overall, it can be concluded that phthalic anhydride is genotoxic *in vitro* at extremely high, cytotoxic concentrations, and only in the absence of a metabolic activation system. This genotoxic effect is not expected to be relevant under *in vivo* conditions, where phthalic anhydride is rapidly hydrolyzed to the non-genotoxic phthalic acid.

No evidence of carcinogenicity was seen in rats after exposure to approximately 1000 mg/kg bw/day of phthalic anhydride, or in male and female mice after exposure to 4670, and 3430 mg/kg bw/day, respectively, in comprehensive chronic (105-week) feeding studies.

There was no fertility study with phthalic anhydride available. No evidence of toxicity to reproductive organs was observed in comprehensive carcinogenicity studies in rats and mice, as no treatment-related changes were observed for any reproductive organ investigated during macroscopic and microscopic examination (NOAEL, rat: 1000 mg/kg bw/day; NOAEL (time-weighted average), mouse: 3430 (f), 4670 (m) mg/kg bw/day). Following i.p. injection which is a route of exposure with unknown relevance for the normal human situation, of doses in the lethal range, developmental toxicity was found in mice in a poorly reported study. However, the chemical is quickly hydrolyzed to phthalic acid after oral, dermal or inhalation exposure. Phthalic acid was investigated in a developmental toxicity feeding study in rats and gave no evidence of embryotoxicity, or fetotoxicity at a non-maternally toxic dose level (1.25 % in feed = approximately 1000 mg/kg bw/day = NOAEL for maternal toxicity). Significant decreases in the weight of male fetuses and in the numbers of ossified centers of the caudal vertebrae were, however, found in the 5.0 % group, where maternal toxicity was also observed (NOAEL, developmental toxicity: 2.5 % in feed = approximately 1700 mg/kg bw/day). Based on the data of phthalic acid, the hydrolysis product of phthalic anhydride, it is concluded that, in the absence of maternal toxicity, phthalic anhydride is not a developmental toxicant.

Environment

Phthalic anhydride forms white flakes or needles with a melting point of about 132 °C. The boiling point is 284.5 °C at 1013 hPa. The density is 1.527 g/cm^3 at 20 °C, the vapor pressure 0.0006 hPa at 26.6 °C, the log K_{OW} = 1.6. The flash point is about 152 °C, and the auto flammability (ignition temperature) is 580 °C. Phthalic anhydride hydrolyzes in water at pH 6.8 - 7.24 with half-lives of 0.5 - 1 min at 25 °C, forming phthalic acid that has dissociation constants of about 2.8 and 5.4. Any phthalic anhydride emitted into the air or into the terrestrial compartment would be rapidly hydrolyzed by humidity in the air or in the soil, respectively.

In the atmosphere phthalic anhydride is degraded by photochemically produced OH radicals. The half-life is calculated to be about 21 days. For phthalic acid a half-life of 13 days is estimated. Removal of phthalic acid in sea water was proved to be influenced by light. Phthalic anhydride is readily biodegradable. In an aquatic ready test system (aerobic) conducted according to OECD TG 301D, > 70 % biodegradation was reported after 30 days for phthalic anhydride as well as for its degradation product, phthalic acid.

Due to the rapid hydrolysis of phthalic anhydride in water, the distribution of the hydrolysis product phthalic acid is calculated. According to the Mackay fugacity model level I, the favorite target compartment of phthalic acid is water with 99.9 %. The calculated Henry's law constants (2.21×10^{-7} Pa m^3/mol at 25 °C for phthalic acid, and 0.64 Pa m³/mol at 25 C for phthalic anhydride) prove a low potential for volatilization from surface waters.

The bioconcentration factors (BCF) of 3.4 for phthalic anhydride and 3.2 for phthalic acid, calculated from the octanol-water partition coefficients, indicate that there is a low potential for bioaccumulation of phthalic anhydride and phthalic acid in aquatic organisms. Tests with ^{14}C-phthalic acid in plants indicate a low potential of phthalic anhydride and phthalic acid for bioaccumulation in plants.

Experimentally obtained adsorption coefficients (K_{oc}) revealed a low sorption potential of phthalic acid. The experimentally achieved K_{oc} values were in the range of 2 to 31 depending on soil properties. In addition, K_{oc} values were calculated with PCKOCWIN v. 1.66 (K_{OC} = 11 for phthalic anhydride, and K_{oc} = 73 for phthalic acid). These results indicate a low sorption potential of phthalic anhydride and phthalic acid onto the organic phase of soil or sediments.

Concerning the toxicity of phthalic anhydride and its hydrolysis product phthalic acid to aquatic species reliable experimental results of tests with fish, *Daphnia*, and algae are available. The result for algae refers both to growth rate and biomass. The tests were performed according to standard procedures or similar methods. The lowest effect values from the aquatic toxicity tests are (n = nominal concentration):

Cyprinus carpio	:48 h-LC_{50}	>500 mg/l (n) (phthalic acid)
Danio rerio	: 7 d-LC_{50}	= 560 mg/l (n)
Oncorhynchus mykiss (*S. gairdneri*)	:60 d-NOEC	= 10 mg/l (n)
Daphnia magna	:24 h-EC_{50}	= 140 mg/l (n) (phthalic acid)
Desmodesmus subspicatus	:72 h-EC_{50}	≥ 100 mg/l (n) (phthalic acid)
Desmodesmus subspicatus	:72 h-NOEC	≥ 100 mg/l (n) (phthalic acid).

Since chronic toxicity tests are available for fish and algae with phthalic anhydride and phthalic acid, respectively, an assessment factor of 50 can be applied using the lowest available effect concentration (NOEC = 10 mg/l) which was obtained for *Oncorhynchus mykiss* (*S. gairdneri*). Calculation yielded a $PNEC_{aqua}$ of 200 µg/l.

Exposure

Phthalic anhydride is produced by oxidation of o-xylene or naphthalene. In 2000, the world wide production volume of phthalic anhydride is estimated to be about 3 232 000 tonnes, with the following regional distribution (tonnes): Western Europe 770 000; Eastern Europe 171 000; USA 485 000; Mexico, South and Central America 249 000; Japan 302 000; Middle East 75 000; other Asia 1 156 000; and others 24 000.

Phthalic anhydride is an important intermediate in the chemical industry. The major subsequent product groups are plasticizers (56 %), unsaturated polyester resins (17 %), and alkyd resins (17 %). Phthalic anhydride is also used as an intermediate in the production of pigments and dyes, agricultural, pharmaceutical, and several other chemical products. Phthalic anhydride containing materials are used in coatings applications for home appliances, automobiles, medical devices and furniture.

Phthalic anhydride is listed in the Swedish and Swiss Product Registers and in the SPIN Database (including consumer products).

The most probable human exposure to phthalic anhydride is through dermal contact or inhalation during manufacture or use. In the Sponsor country, exposure is controlled in occupational settings. Consumers may be exposed to phthalic anhydride from the use of plastics, furniture, glues, coatings and home products from which phthalic anhydride may leach. Consumers may be exposed to (non-synthetic) phthalic anhydride from natural flavor and oak smoke. Oak smoke and its aqueous preparations are used in the production of several smoked foods and alcoholic beverages. Phthalic anhydride is reported to occur in the volatile flavor of baked potatoes, in spent chlorination liquor from sulphite bleaching, in a hazardous waste dump in Northern Spain, and in sediments of San Diego Bay after sediment pyrolysis. There is no study which unambiguously demonstrates that phthalic anhydride may occur in environmental waters or drinking water (phthalic anhydride may be formed as an artifact during gas chromatographic analysis). Phthalic anhydride is present in ambient air, fly ash, diesel exhaust, oak smoke, and pyrolysis products.

The Sponsor company manufactures phthalic anhydride in closed systems. During production virtually no phthalic anhydride is emitted into the atmosphere (< 25 kg/a) and into environmental waters.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is a candidate for further work. The chemical possesses properties indicating a hazard for human health (irritation of skin and respiratory system, serious eye damage, respiratory and skin sensitization). Based on data presented by the Sponsor country, adequate risk management measures are being applied for occupational settings. A potential for consumer exposure exists as a result of its use in plastics, furniture and home products. It is therefore recommended to perform an exposure assessment and, if then indicated, a risk assessment.

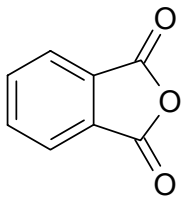
Environment: This chemical is currently of low priority for further work because of its low hazard profile.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 85-44-9
IUPAC Name: **Phthalic anhydride**
Molecular Formula: $C_8H_4O_3$
Structural Formula:



Molecular Weight: 148.12 g/mol
Synonyms: Phthalic acid anhydride
1,3-Isobenzofurandione
Isobenzofuran-1,3-dione
1,2-Benzenedicarboxylic acid anhydride
1,2-Benzenedicarboxylic anhydride
1,3-Dihydro-1,3-dioxoisobenzofurane
1,3-Dioxophthalane
1,3-Phthalandione
Phthalandione
Isobenzofurane, 1,3-dihydro-1,3-dioxo-

1.2 Purity/Impurities/Additives

Purity of the commercial product: ≥ 99.8 % (determined by GC) (Lorz, Towae, and Bhargava, 2002)

Impurities:

- Maleic anhydride ≤ 0.05 % (specification limit, determined by GC) (Lorz, Towae, and Bhargava 2002)
- Benzoic acid ≤ 0.1 % (specification limit, determined by GC) (Lorz, Towae, and Bhargava 2002)
- Phthalic acid ≤ 0.1 % (specification limit) (BASF AG, 2000)
- Naphthoquinone (historic data, technical product in the early 1950ies; Oettel, 1955)

1.3 Physico-Chemical properties

Table 1 Summary of physico-chemical properties of phthalic anhydride

Property	Value	Reference	IUCLID
Substance type	Organic		1.1.1
Physical state	White flakes or needles	Lorz, Towae, and Bhargava, 2002	1.1.1
Melting point	131.6 °C	Lorz, Towae, and Bhargava, 2002	2.1
Boiling point	284.5 °C*	MITI, 1992	2.2
Relative density	1.527 g/cm^3 at 20 °C	Beilstein, 2003	2.3
Vapour pressure	0.0006 hPa at 26.6 °C	Crooks and Feetham, 1946	2.4
Partition coefficient n-octanol/water (log K_{ow})**	1.6	NIOSH, 2003	2.5
Water solubility**	16400 mg/l	Lorz, Towae, and Bhargava, 2002	2.6.1
Flash point	152 °C	NIOSH, 2003	2.7
Auto flammability (ignition temperature)	580 °C	Lorz, Towae, and Bhargava, 2002	2.8
Dissociation constant	pK_{a1} = 2.76 at 25 °C***	Serjeant and Dempsey, 1979	2.12
	pK_{a2} = 5.41 at 25 °C***	Hamer and Acree, 1945	2.12

*Pressure for the boiling point is not reported but assumed to be 1013 hPa. **Rapid hydrolysis to phthalic acid ***Phthalic acid

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

Phthalic anhydride is predominantly produced by oxidation of o-xylene or, in minor amounts, of naphthalene (Weissermel and Arpe, 1996):

CH_3-C_6H_4-CH_3 + 3 O_2 → $C_8H_4O_3$ + 3 H_2O

2 $C_{10}H_8$ + 9 O_2 → 2 $C_8H_4O_3$ + 4 H_2O + 4 CO_2

In 2000, the world wide production volume of phthalic anhydride is estimated to be about 3 232 000 tonnes (Bizzari, 2001).

Table 2 Estimated production volume in 2000 (Bizzari, 2001).

Region	Estimated production volume (tonnes/a)
Western Europe	770 000
USA	485 000
Japan	302 000
Eastern Europe	171 000
Mexico / South / Central America	249 000
Middle East	75 000
Other Asia	1 156 000
Others	24 000

Phthalic anhydride is mainly used as an intermediate in chemical processes (Bayer Chemicals, 2004).

The major subsequent product groups are

- Plasticizers (56 %):
  Phthalate esters like dioctylphthalate, C7-C11 linear phthalates, diisodecyl phthalate, diisononylphthalte, n-butyl benzyl phthalate
- Unsaturated polyester resins (17 %):
  Formed by polycondensation using unsaturated dicarboxylic acid, diols, and aromatic dicarboxylic acid
- Alkyd resins (17 %):
  Reaction of polybasic acids or anhydrides (e.g. phthalic anhydride), polyhydric alcohols, and fatty oils or acids
- Other uses (10 %):
  Intermediate in the production of
  - polyester polyols
  - isatoic anhydride
  - intermediates for pigments and dyes
  - flame retardants for polyesterpolyols
  - intermediates in the agricultural and pharmaceutical sector

(estimation according to Bizzari, 2001).

EPA (1994) reports several uses of phthalic anhydride in chemical synthesis, e.g. to make halogenated anhydrides, polyester polyols for urethanes, phthalocyanine pigments, dyes, pharmaceuticals; tanning and curing agents, solvents, and various chemical intermediates. Informations from the Nordic and Swiss Product Registers are discussed in Chapter 2.3.2.

2.2 Environmental Exposure and Fate

2.2.1 Sources of Environmental Exposure

Environmental information from manufacturing and processing of phthalic anhydride is available for the Bayer Chemicals plants in Germany (Bayer Chemicals, 2004).

At the Bayer sites phthalic anhydride is manufactured in closed systems (Bayer Chemicals, 2004).

The exhausts from manufacturing and processing are connected to thermal exhaust purification plants and air washing units. Thus, at Bayer Chemicals, during production virtually no phthalic anhydride is emitted into the atmosphere. In 2000, according to the current Official Emission Declaration, virtually no phthalic anhydride (< 25 kg/a) was emitted into the atmosphere (Bayer Chemicals, 2004).

The wastewater from manufacturing and processing is led to Bayer-owned industrial wastewater treatment plants (Bayer Chemicals, 2004).

The air and water emissions of the Bayer production sites are monitored by Environmental Surveillance Groups which operate independently of any manufacturing unit. Since phthalic anhydride hydrolyzes rapidly under the conditions in the wastewater treatment plants, the hydrolysis product phthalic acid is monitored. Phthalic acid is readily biodegradable, and the potential for phthalic acid biodegradation is widespread throughout sewage organisms. Within this daily monitoring program phthalic acid was not detected in the effluents of the wastewater treatment plants with detection limits of 50 and 500 µg/l, respectively (Bayer Chemicals, 2004).

The effluents of the Bayer wastewater treatment plants passes into the river Rhine, with a 10 percentile of the river flow of 1050 m^3/s at both sites. For the first site, with the dilution factor of > 1000 (according to TGD, a maximum value of 1000 was used) and the detection limit of 50 µg/l, for the receiving water a local

Predicted Environmental Concentration (PEC_{local}) of < 0.05 µg/l

is calculated for phthalic acid. Taking into account the dilution factor of 700 and the detection limit of 500 µg/l, for the receiving water at the second site, a local

Predicted Environmental Concentration (PEC_{local}) of < 0.7 µg/l

is calculated for phthalic acid (Bayer Chemicals, 2004).

In a (historic) review on air emissions potential of phthalic anhydride manufacturing Fawcett (1970) reports phthalic anhydride concentrations of 40 - 200 ppm in exhaust gases prior to abatement. According to the Toxic Release Inventory of the USA, approximately 340 tonnes of phthalic anhydride were released from certain US industries into the air, and approximately 2 tonnes of phthalic anhydride into environmental waters in 1992 (EPA, 1994). In 2001, the releases into the air had decreased to approximately 120 tonnes/a of phthalic anhydride and there were no releases into environmental waters (EPA, 2004).

2.2.2 Photodegradation

There are no experimental data on the stability of phthalic anhydride in the atmosphere.

The calculated half-life of phthalic anhydride in air due to indirect photodegradation is 21 days, considering a daily mean OH-radicals concentration of 500 000 radicals cm^{-3} (Bayer Industry Services, 2004a).

The determination of this endpoint is not suitable, since phthalic anhydride will be affected by air humidity, which leads to hydrolysis of the substance. The hydrolysis product is phthalic acid. The half-life of phthalic acid is estimated to be about 13 days due to indirect photodegradation in the atmosphere (Bayer Industry Services, 2004b).

In sea water at 50 °C, Armstrong and Tibbitts (1968) measured a first order rate constant for photooxidation of phthalic acid of about 0.75 h^{-1} that is equivalent to a half-life of 0.93 hours. At room temperature, the photooxidation is expected to proceed more slowly.

The data on photodegradation are listed in Table 3.

Table 3 Photodegradation of phthalic anhydride and phthalic acid (IUCLID 3.1.1)

Substance	Parameter	Method	Result	Reference
Phthalic anhydride	Indirect photodegradation in air	Calculation for 24 h-day; 500,000 OH/cm^3	$t_{½}$ = 21 d	Bayer Industry Services, 2004a
Phthalic acid	Indirect photodegradation in air	Calculation for 24 h-day; 500,000 OH/cm^3	$t_{½}$ = 13 d	Bayer Industry Services, 2004b
Phthalic acid	Influence of light in the degradation of phthalic acid in seawater	Radiation apparatus with a 380 W mercury arc	$t_{½}$ = 0.93 h	Armstrong and Tibbitts, 1968

2.2.3 Stability in Water

Phthalic anhydride hydrolyzes rapidly in the presence of water forming phthalic acid. Experiments with phthalic anhydride were performed in the presence of buffer. Andres, Granados and Rossi (2001) determined experimentally a half-life for phthalic anhydride of 30.5 seconds at pH 7.24. At pH 6.8 the half-life of phthalic anhydride in water was prolonged to 61 seconds (Table 4).

Regarding natural systems, the impact of phthalic acid depends on the buffer capacity of the system. Buffer function is attributed to humic substances, alkaline earth carbonates, clay minerals, silicates, as well as atmospheric oxides. Phthalic acid is a weak dibasic acid whose pK_{a1} is 2.76 (Serjeant and Dempsey, 1979) and pK_{a2} is 5.41 at 25 °C (Hamer and Acree, 1945).

Table 4 Hydrolysis of phthalic anhydride in different buffer-systems (IUCLID 3.1.2)

Procedure	Result	Reference
Abiotic degradation in phosphate buffered system	at pH 7.24, 25 °C $t_{½}$ = 30.5 sec	Andres, Granados and Rossi, 2001
Abiotic degradation in N-methyl imidazole buffered system	at pH 6.8, 25 °C $t_{½}$ = 61 sec	Andres, Granados and Rossi, 2001

2.2.4 Transport between Environmental Compartments

Due to the rapid hydrolysis of phthalic anhydride (*cf.* Chapter 2.2.3) a transport of the substance between environmental compartments is unlikely to occur.

Calculations of the Henry's law constant (HLC) and of the distribution of phthalic anhydride in the environment according to the Mackay fugacity model, are hypothetical in that the substance hydrolyzes rapidly in water. The Mackay model does not consider degradation reactions, hence the Mackay equilibrium distribution of phthalic anhydride in the environment is not appropriate.

The hydrolysis product of phthalic anhydride, phthalic acid, is a weak dibasic acid whose pK_{a1} is 2.8 and pK_{a2} is 5.41 at 25°°C. Although phthalic acid dissociates in neutral, dilute solution, the distribution of phthalic acid in a "unit world" was calculated according to the Mackay fugacity model level I (Table 5). The main target compartment of phthalic acid is water with 99.9 % (Bayer Industry Services, 2004b).

Table 5 Input parameters and results for phthalic acid of the Mackay Fugacity Model Level I (IUCLID 3.3.2)

Input Parameters	Value
Temperature	25 °C
Vapour Pressure	8.48 x 10^{-5} Pa
Water Solubility	7010 mg/l
Log K_{ow}	0.73
Melting Point	191 °C

Compartment	Calculated distribution
Water	99.91 %
Air	< 0.001 %
Sediment	0.043 %
Soil	< 0.042 %
Suspended Sediment	< 0.001 %
Aerosol	< 0.001 %
Aquatic Biota	< 0.001 %

The Henry's law constant (HLC) of phthalic anhydride is calculated as 0.64 Pa m³/mol at 25 °C (Bayer Industry Services, 2004a). This data indicates that phthalic anhydride is essentially non volatile from aqueous solution according to the criteria of Thomas (1990).

For the hydrolysis product of the phthalic anhydride, phthalic acid, the HLC is estimated as 2.21×10^{-7} Pa m³/mol (Bayer Industry Services, 2004b). This value indicates that phthalic acid is non volatile in water (Table 6).

Table 6 Distribution in water-air (IUCLID 3.3.2)

Substance	Property	Method	Value	Reference
Phthalic anhydride	Fugacity Water – air Henry's law constant for phthalic anhydride	Bond-Method (calculated at 25 °C)	0.64 Pa m³/mol	Bayer Industry Services, 2004a
Phthalic acid	Fugacity Water – air Henry's law constant for phthalic acid	Bond-Method (calculated at 25 °C)	2.21×10^{-7} Pa m³/mol	Bayer Industry Services, 2004b

2.2.5 Biodegradation

Based on the available experimental biodegradation test results for phthalic anhydride, the substance is classified as readily biodegradable. Table 7 compiles the relevant data on biodegradation of phthalic anhydride.

In a modified MITI test comparable to OECD TG 301 C the biodegradation of phthalic anhydride was investigated (Sasaki and Hutzinger, 1978; MITI, 1992). After 2 weeks 85 % degradation of the test substance was determined.

The biodegradation of phthalic anhydride was also investigated with activated sludge obtained from the waste water treatment plant of the Kashima petroleum and petrochemical industrial complex in Japan. The inoculum was therefore well acclimated to organic substances. The test was performed in a "fill-and-draw" type apparatus with aeration cylinders. TOC and COD were monitored during the test. After 24 hours, 33 % degradation was measured with COD and 88 % with TOC (Matsui et al., 1975; Matsui, Okawa, and Ota, 1988).

In a closed bottle test (OECD TG 301 D) with predominantly domestic sewage the biodegradation of phthalic anhydride and phthalic acid was investigated. After 30 days more than 70 % degradation of both test substances were determined (Bayer AG, 1972; Bayer AG, 1973).

Table 7 Tests on biodegradation of phthalic anhydride and phthalic acid (IUCLID 3.5)

Substance	Inoculum	Procedure	Biodegradation	Reference
Phthalic anhydride	Activated sludge	Comparable to OECD TG 301C. Only raw data available	85.2 % after 14 d	MITI, 1992
Phthalic anhydride	Aerobic activated sludge	Comparable to OECD TG 301C	well-biodegradable	Sasaki and Hutzinger, 1978
Phthalic anhydride	Aerobic activated sludge, industrial	"fill-and-draw" type apparatus	33 % TOC removal 88 % COD removal after 24 h	Matsui et al., 1975; Matsui, Okawa, and Ota, 1988
Phthalic anhydride	Predominantly domestic sewage	OECD TG 301D	71 % after 30 d	Bayer AG, 1972
Phthalic acid	Predominantly domestic sewage	OECD TG 301D	74 % after 30 d	Bayer AG, 1973

2.2.6 Bioaccumulation

Since phthalic anhydride hydrolyzes rapidly in water (*cf*. Chapter 2.2.3), no bioconcentration factor (BCF) can be measured.

Taking in account the octanol-water partition coefficient, a BCF has been calculated with the BCF Program (v 2.15). Using the log K_{OW} of 1.6 for phthalic anhydride, the calculated BCF is 3.4 (Bayer Industry Services, 2004a).

For the hydrolysis product phthalic acid, a BCF value of 3.2 is calculated by using the log K_{OW} of 0.73 (Bayer Industry Services, 2004b).

These results indicate no significant potential for bioaccumulation of phthalic anhydride and phthalic acid in aquatic organisms.

In green house studies ^{14}C-phthalic acid was applied to soil planted with wheat (*Triticum aestivum*)/corn (*Zea mays*) or soybeans (*Glycine max*)/tall fescue (*Festuca arundinacea*). Only a small part of the ^{14}C applied to the soil was recovered from the plants and soil (up to 6 %). The mean bioaccumulation ratios for total ^{14}C were 0.003 for plants and 0.0005 for seeds. For phthalic acid the bioaccumulation ratios were 0.013 for plants and 0.0046 for seeds. TLC analysis showed that the percent of the extractable ^{14}C still in phthalic acid, was 5 % in corn and fescue, 15 % in soybean, 9 % in wheat plants, and the highest for wheat seed (47 %) (Dorney et al., 1985). This study demonstrates the relatively low potential for accumulation of phthalic acid in plants.

Phthalic acid is a dibasic acid whose pK_{a2} is 5.41 at 25 °C (Hamer and Acree, 1945). The ionisation implies that phthalic acid does not accumulate in organisms.

Table 8 Bioaccumulative properties of phthalic anhydride and phthalic acid (IUCLID 3.7)

Parameter	Method	Result	Source
Phthalic anhydride Bioconcentration factor	Calculated	BCF = 3.4	(Bayer Industry Services, 2004a)
Phthalic acid Bioconcentration factor	Calculated	BCF = 3.2	(Bayer Industry Services, 2004b)

2.2.7 Geoaccumulation

Since phthalic anhydride hydrolyzes rapidly in water (*cf.* Chapter 2.2.3), no experimental data can be obtained.

The distribution of phthalic anhydride and phthalic acid between the organic phase of soil or sediments and the porewater was calculated by using QSAR with the PCKOC program (v 1.66). A K_{OC} of 11 for phthalic anhydride (Bayer Industry Services, 2004a) and of 73 for phthalic acid (Bayer Industry Services, 2004b) was calculated.

Von Oepen, Koerdel, and Klein (1991) investigated the sorption capacity of three different soils by batch equilibrium studies for phthalic acid. The soils used for testing were an acidic forest soil, an agricultural soil and a sublimnic soil. The sorption equilibrium was reached within 16 hours. Sorption coefficients between 2 and 31 were determined. The experimental K_{OC} values suggest that phthalic acid has a high mobility in soil.

According Litz (1990) the experimental and calculated values indicate that phthalic anhydride and phthalic acid are supposed to have a slight geoaccumulation potential.

2.2.8 Environmental Monitoring

Phthalic anhydride has been reported from several environmental samples and materials which contain enough water to hydrolyze phthalic anhydride. In regard to an air sample the US EPA noted that the presence of the phthalic anhydride could have resulted from the hydrolysis of phthalate esters followed by thermal dehydration in the GC injection port (EPA, 1994).

Similarly, Vainiotalo and Pfaeffli (1990) observed that both PVC (polyvinylchloride) containing DEHP (di-2-ethylhexylphthalate) as well as pure DEHP released phthalic anhydride which was formed during DEHP degradation at high temperatures (≥ 180 °C).

Thus, the significance of several studies using GC techniques with phthalates exposed to high temperatures is rather limited because phthalic anhydride may be formed during these analytical procedures.

Occurrence

Phthalic anhydride is reported to be present in the volatile flavor of Idaho potatoes baked in aluminium foil at 205 °C for 105 min (Coleman, Ho, and Chang, 1981).

Waste/soil/sediments

In three insufficiently documented studies with significant methodological deficiencies, phthalic anhydride was reported to be present in spent chlorination liquor from bleaching of sulphite pulp

(0.2 - 0.4 mg/kg) (Carlberg, Drangsholt, and Gjos, 1986), insediment cores of an uncontrolled hazardous waste dump in Northern Spain (Villanueva, Rosell, and Grimalt, 1991), and in PAH contaminated sediments of San Diego Bay area (Deshmukh, Chefetz, and Hatcher, 2001).

Since phthalic anhydride is formed from phthalates at less than 200 °C (Vainiotalo and Pfaeffli, 1990), or during pyrolysis (as performed by Deshmukh, Chefetz, and Hatcher, 2001), it is possible that phthalic anhydride was formed during GC/MS analysis.

Water

There are some historic data on the occurrence of phthalic anhydride in water samples. Some few studies found phthalic anhydride in water samples. However, the water samples examined contained several organic phthalates and or phthalic acid. Since phthalic anhydride is formed from phthalates at less than 200 °C (Vainiotalo and Pfaeffli, 1990), and phthalic anhydride can also be formed from phthalic acid, it is possible that phthalic anhydride was formed during analysis.

The wastewater treatment plant of the Kashima petroleum and petrochemical industrial complex (Japan) has a hydraulic retention time of approximately 14 h (Matsui et al., 1975; Matsui, Okawa, and Ota, 1988). 88 % of the TOC of phthalic anhydride (influent concentration 65 mg/l) was removed from the authentic wastewater within 24 h during experimental incubations (*cf.* Chapter 2.2.6). However, since the half-life of phthalic anhydride in aqueous solution is in the range of seconds to few minutes, it is assumed that not phthalic anhydride but phthalic acid persisted and that phthalic acid was the source of phthalic anhydride formed during analysis.

The influent of the Prato (Italy) municipal wastewater treatment plant contained phthalic anhydride, but not the effluent (Lepri, Desideri, and Del Bubba, 1997).

Phthalic anhydride was found in groundwater after distribution for drinking purposes, but not in the same groundwater before distribution (Fielding et al., 1981). No phthalic anhydride could be detected in 12 other raw waters of the UK. Unfortunately, the authors do not report on the distribution method. Since several other compounds (e.g. benzyl cyanide, 2 C_4 alkyl benzenes) stemmed from the distribution process, it appears that the phthalic anhydride was formed during GC/MS analysis from phthalates or phthalic acid contaminating the groundwater during the distribution process.

In 15 out of 85 contaminated water streams of the USA, phthalic anhydride was detected with an estimated maximum of 1 µg/l and a median of 0.7 µg/l in positive samples (limit of detection 0.25 µg/l) (Kolpin et al., 2002). Since phthalic anhydride was encountered routinely also in laboratory blanks (Kolpin et al., 2002), it is not clear whether phthalic anhydride was present in the tested US waters.

Guzzella and Sora (1998) report that phthalic anhydride and several phthalates were detected in the three large Italian lakes (Como, Garda, and Maggiore) in 1991 and 1992. Unfortunately, the study was not printed correctly, and its reliability cannot be elucidated.

The EPA (1994) reports that phthalic anhydride has been identified, but not quantified, in US drinking water. However, they concluded that the rapid hydrolysis of phthalic anhydride to phthalic acid that occurs in aqueous media, would preclude any significant transport of the chemical in the aquatic environment. The EPA was also concerned on the formation of artifacts (see Air/aerosols).

There are no reports on the occurrence of phthalic anhydride in environmental media in the Sponsor country.

Air/aerosols

In his compilation of chemical compounds in the atmosphere Graedel (1978) lists phthalic anhydride as an air pollutant. Sasaki et al. (1997) report that phthalic anhydride is formed during atmospheric photooxidation of naphthalene in the gas phase. It is also formed during photooxidation of adsorbed naphthalene (Brussol et al., 1999).

Ramdahl, Becher, and Bjorseth (1982) reported phthalic anhydride to occur in urban air particles from St. Louis (MO, USA), after fractionation by HPLC, and analysis by GC/MS. Yokouchi and Ambe (1986) identified both phthalic anhydride and phthalic acid by GC/MS in aerosols collected north of Tokyo in 1985. Phthalic anhydride was reported from arctic air at a concentration of 10 ng/m^3, but it was later noted that the presence of the anhydride could have resulted from the hydrolysis of phthalate esters followed by dehydration in the GC injection port (EPA, 1994).

Using the US National Ambient VOC Data Base, Kelly et al. (1994) reported that phthalic anhydride was detected at one location (not specified) with more than 10 samples (no method reported). Phthalic anhydride concentration was less than 6 µg/m^3. The half life of phthalic anhydride in air was estimated to be longer than 5 days.

Phthalic anhydride was tentatively identified in aerosols collected in Los Angeles in 1993. Tentative phthalic anhydride concentrations were reported to be 5.9 mg/kg of extractable organic carbon (EOC). From the annual average of the ambient EOC concentration (8.89 µg/m^3), a phthalic anhydride concentration of 52 pg/m^3 was tentatively calculated for the Los Angeles aerosol (Hannigan et al., 1998).

In 4 air samples collected over landfills the concentrations of phthalic anhydride were 0.06 ppb, 0.16 ppb, and 2 samples were below the detection limit of < 0.06 ppb. No phthalic anhydride was detected in several air samples of the vicinity of these landfills (Davoli et al., 2003).

Phthalic anhydride was present in fly ash from a municipal solid waste incinerator (Akimoto et al., 1997). It was also identified with 2 different GC/MS methods in diesel exhaust particles (Bayona, Markides, and Lee, 1988).

Phthalic anhydride (and more than 200 other organic compounds including e.g. ketones, esters, acids, furans, pyrans, and aryl ethers) were detected in aqueous oak smoke preparations (Guillén and Manzanos, 2002).

Phthalic anhydride is also reported to occur in the organic compounds extracted from weathered surfaces of Saxonean sandstone from historic buildings in the city of Dresden, Germany (Machill et al., 1997). Potential sources of phthalic anhydride include microorganisms in these surfaces, but - although not discussed in detail – the more likely source being deposition of air contaminants. Phthalic acid and phthalates were also present in the extracts. Since the injector for the GC was held at 250 °C, formation of phthalic anhydride from these compounds cannot be excluded.

Phthalic anhydride was mentioned to be a trace component in the emissions from hydrocarbon based wood stains for indoor materials (0 - 2 mg/g of ready-to-use wood stain) (Zhu, Zhang, and Shaw, 1999). However, in this study no measures were reported to avoid the formation of phthalic anhydride from phthalates during analysis (GC/MS).

Phthalic anhydride was detected as a thermolytic degradation product of steel protective paint. Steel plates coated with primer or finishing paint yielded up to 0.88 g phthalic anhydride/m^2 upon heating at 350 °C (Henriks-Eckerman, Engstroem, and Anaes, 1990).

The data on environmental occurrence of phthalic anhydride are compiled in the following Table.

Table 9 Reported environmental occurrence of phthalic anhydride

Medium	Matrix	Phthalic anhydride	Source	Reliability
Biota	volatile flavor of baked potatoes	+	Coleman, Ho, and Chang, 1981	2
Liquid waste	Spent chlorination liquor from bleaching of sulphite pulp	0.2 - 0.4 mg/kg	Carlberg, Drangsholt, and Gjos, 1986	3
Sediment	Sediment cores of an uncontrolled hazardous waste dump in Northern Spain	+	Villanueva, Rosell, and Grimalt, 1991	3
Sediment	Contaminated sediments of San Diego Bay area	+	Deshmukh, Chefetz, and Hatcher, 2001	3
Wastewater	Wastewater treatment plant of Kashima industrial complex, Japan	+ influent - effluent	Matsui et al., 1975; Matsui, Okawa, and Ota, 1988	both 2
Wastewater	Prato (Italy) municipal wastewater treatment plant	+ influent - effluent	Lepri, Desideri, and Del Bubba, 1997	2
Water	Surfacewater and groundwater in the UK	+ in 1 out of 14 samples	Fielding et al., 1981	2
Drinking water	US drinking water	-	EPA, 1994	2
Surface water	contaminated US water streams	+ in 15 out of 85 samples	Kolpin et al., 2002	4
Surface water	3 Italian lakes in 1991 and 1992	+	Guzzella and Sora, 1998	4
Air	Polluted air	+	Graedel, 1978	4
Air	Formation from organics in polluted air,	Formed from organic pollutants	Sasaki et al. (1997)	2
Air/aerosols	Aerosol	Formed on surfaces	Brussol et al., 1999	2
Air/aerosols	Urban air particles from St. Louis (MO, USA),	+	Ramdahl, Becher, and Bjorseth, 1982	4
Air/aerosols	Aerosols collected north of Tokyo in 1985	+	Yokouchi and Ambe, 1986)	4
Air	Arctic air	Not clear	EPA, 1994	2
Air/aerosols	Background concentration	6 µg/m^3 (median)	Kelly et al., 1994	4
Air/aerosols	Aerosols collected in Los Angeles in 1993	5.9 mg/kg extractable organic carbon	Hannigan et al., 1998	2
Air	Air over landfills and in their vicinity	+ over landfills - vicinity of landfills	Davoli et al., 2003	4
Exhausts	fly ash from a municipal solid waste incinerator	+	Akimoto et al., 1997	2
Exhausts	diesel exhaust particles	+	Bayona, Markides, and Lee, 1988	2
Food	oak smoke preparations	+	Guillén and Manzanos, 2002	2

Table 9 (cont.) Reported environmental occurrence of phthalic anhydride

Medium	Matrix	Phthalic anhydride	Source	Reliability
Air	weathered surfaces of Saxonean sandstone from historic buildings in the city of Dresden, Germany	+	Machill et al., 1997	4
Air	emissions from hydrocarbon based wood stains	0-2 mg/g of ready-to-use wood stain	Zhu, Zhang, and Shaw, 1999	4
Air	thermolytic degradation product of steel protective paint	0.88 g phthalic anhydride/m^2	Henriks-Eckerman, Engstroem, and Anaes, 1990	2

+ indicates that it is reported that phthalic acid is present in matrix, - denotes not detected

2.3 Human Exposure

2.3.1 Occupational Exposure

Occupational exposure to phthalic anhydride is most likely to occur through inhalation and dermal contact. In 1981 - 1983 approximately 81 000workers were potentially exposed to phthalic anhydride in the USA (NIOSH, 2005).

Workplaces

At the Bayer manufacturing sites, workplaces where phthalic anhydride is manufactured or processed (Bayer Chemicals, 2004), include

- Manufacturing processes: Oxidation of o-xylene to phthalic anhydride, distillation (*cf* Chapter 2.1)
- Processing: In chemical synthesis, *e.g*. production of chemical intermediates.

At the Bayer sites, phthalic anhydride is manufactured in closed systems (*cf* Chapter 2.2.1). Phthalic anhydride is transported in rail or road tankers (Bayer Chemicals, 2004). Bayer participates in the German TUIS (Transport-Unfall und Informations System) for support in case of accidents involving chemicals; TUIS is part of the European Emergency Response Network of CEFIC (2002). In the plastics processing industries phthalate esters are often used as plasticizers in PVC (poly-vinylchloride). Phthalic anhydride may be formed during thermal phthalate degradation (*cf.* Chapter 2.2.8).

Precautionary measures at the workplace

In accordance with national regulations and the principles of Responsible Care and Sustainable Development, at Bayer Chemicals the exposure of workers is reduced to the lowest technically practicable level (Bayer Chemicals, 2004).

Surveys of the Bayer workplaces are performed according to German Technical Guidances TRGS 402 and TRGS 901. This includes regular surveys in the working area for any possible exposure to hazardous substances and phthalic anhydride under all relevant work scenarios, and encompasses appropriate control measures (Bayer Chemicals, 2004).

To protect workers from exposure, several precautionary and protective measures are taken. Sampling, for instance, is performed with specially designed systems and filling operations take place in a closed system with special suction devices. Repair and maintenance work is only carried out on parts of the manufacturing or processing systems which have been emptied. Prior to repair and maintenance the parts are flushed with water or alkali to remove residual substances. Special written permits are required which include a detailed description of the protective measures depending on the work to be done (e.g. full protective clothing and gas filter masks (classification ABEK)) (Bayer Chemicals, 2004).

Down stream users of phthalic anhydride are informed on the recommended safety measures through a material safety data sheet (Bayer Chemicals, 2004).

Potential exposure at the workplace

In Germany for occupational settings, the maximum permissible concentration set for phthalic anhydride particulate matter in the air at the workplace (MAK) of 1.0 mg/m³ (respirable fraction) (TRGS 900, 2004) was recently withdrawn by the MAK commission (DFG, 2001). At Bayer Chemicals production and processing sites, the exposure of workers is below 1.0 mg/m^3 (Bayer Chemicals, 2004).

In 2 alkyd and/or saturated polyester resin plants (*cf* Chapter 3.1.4), time-weighted average concentrations of phthalic anhydride dust were 2.8 and 4.9 mg/m^3 during manual loading of reactors from paper bags, 6.1 and 13 mg/m^3 during handling of emptied paper bags, and <0.3 and 0.3 mg/m^3 during cleaning, respectively. In one of the plants, also the dust concentration was determined during general work (including sampling from reactor, 0.15 mg/m^3) and in the canteen (< 0.1 mg/m^3). 40 - 46 % of the dust was in the respirable dust fraction (Wernfors et al., 1986).

Also in alkyd and/or saturated polyester resin plants, working place air concentrations of phthalic anhydride were 6.6 mg/m^3 (range 1.5 - 17 mg/m^3) during phthalic anhydride loading of reactors (Nielsen et al., 1991).

In 6 PVC plastics processing plants using PVC containing organic phthalates as plasticizers, the workplace air concentrations of phthalic anhydride (and DEHP in 9 plants) were determined (Vainiotalo and Pfaeffli, 1990). Phthalic anhydride levels ranged from below the detection limit (<0.02 µg/m^3) to 5 µg/m^3. For comparison, the phthalate levels were up to 100 times higher (< 0.02 - 0.5 mg/m^3). Use of heat sealers may therefore expose users of PVC film to phthalic anhydride (SRC, 1995).

Due to formation from components of alkyd paint, phthalic anhydride may be released during welding or flame cutting of alkyd coated metal (Henriks-Eckerman, Engstroem, and Anaes, 1990).

Biological monitoring

Phthalic anhydride specific immunoglobin E (IgE) was detected by a radio-allergosorbent test (RAST) in the serum of a chemical worker with hypersensitivity to phthalic anhydride (Maccia et al., 1976).

Severe immunoreactions were observed in 2 industrial workers exposed to phthalic anhydride dust for 3 months and for 35 years, respectively. The phthalic anhydride specific IgE levels in these 2 workers and in 2 other workers cross-sensitized with the structurally related anhydrides, hexahydro phthalic anhydride and himic anhydride, were 10 - 12-fold compared to a control group of 30 unexposed persons (Bernstein et al., 1984).

The presence of serum IgE antibodies to phthalic anhydride was demonstrated in 4 workers out of 54 exposed occupationally to phthalic anhydride dust in alkyd and/or saturated polyester resin plants (*cf* Chapter 3.1.4) (Wernfors et al., 1986).

Compared to controls, the levels of IgG specific to phthalic anhydride human serum albumin adducts were 4 - 6-fold in exposed workers e.g. a lab technician testing the quality of phthalic anhydride. Consistently, in exposed workers, the levels of IgE were increased 2 - 6-fold (Bernstein, Patterson, and Zeiss, 1982).

The levels of serum IgE antibodies to phthalic anhydride determined with RAST were similar in workers exposed to phthalic acid and in controls. However, the total IgE level in workers of 32 kilounits/liter (ku/l) was twice the level in controls (15 ku/l). Determined with an enzyme-linked immunosorbent assay (ELISA), the level of specific antibodies against phthalic anhydride antigen (IgG) were 0.21 OD in workers, to 0.12 OD in controls (Nielsen *et al*., 1991). In another study, the RAST values of 3 workers exposed to phthalic anhydride were 6, 13, and 34 compared to < 0.3 in controls, indicating high antibody levels against phthalic anhydride in these workers (Welinder and Nielsen, 1991).

Baur *et al*. (1995) examined a group of 96 workers exposed to several acid anhydrides, including phthalic anhydride, in 2 German chemical plants. 9 workers with clinical allergic symptoms and 2 without clinical allergic symptoms, had IgE levels higher than 0.35 ku/l in an enzyme-allergo-sorbent test, and 48 symptomatic workers and 42 asymptomatic workers had IgE levels of less than 0.35 ku/l.

In a US factory manufacturing phthalic anhydride, di(2-ehtylhexyl)phthalate, and other phthalates, pronounced increases of urinary phthalate concentrations occurred only in chemical operators during shift. Since the urine samples were hydrolyzed and determined as dimethylphthalate, it cannot be distinguished between the molecular species potentially present in urine, e.g. phthalic anhydride, phthalic acid, di(2-ethylhexyl)phthalate, or mono(2-ethylhexyl)phthalate. However, by additional examinations, neither di(2-ethylhexyl)phthalate, nor mono(2-ethylhexyl)phthalate could be detected in urine samples. There was no correlation between the increase in urinary phthalate concentrations and the workplace air concentrations of phthalic anhydride and/or of di(2-ethylhexyl)phthalate. The results of the biological monitoring of total phthalate in urine of three exposure groups are presented in Table 10. One of the highest post-shift phthalate concentration occurred in an administrator who was unlikely to be exposed during work. The pre-shift urinary phthalate concentration of this administrator was actually higher than his post-shift value (Liss et al. 1985).

Table 10 Urinary phthalate concentrations in workers of a phthalic anhydride manufacturing and processing plant (Liss et al., 1985)

Exposure	High exposure, with detectable airborne phthalic anhydride in personal sample*	High exposure, without detectable airborne phthalic anhydride in personal sample*	Control (low exposure)*
Preshift Number of participants	26	20	41
Urinary phthalate concentrations (mean, µmol/l)	5.6 ± 3.4	4.9 ± 6.1	6.4 ± 6.7
Postshift Number of participants	27	19	40
Urinary phthalate concentrations (mean, µmol/l)	9.9 ± 8.7	6.8 ± 8.1	5.9 ± 5.8

* ± Standard deviation

2.3.2 Consumer Exposure

Consumers may be exposed to phthalic anhydride via the environment by inhalation e.g. of the volatile flavor of baked potatoes and of atmospheric aerosols (*cf.* Chapter 2.2.8).

Phthalic anhydride is used as an intermediate for making polyesters, polyurethane resins, and plasticizers. The resulting materials are used in coatings applications for home appliances, automobiles, medical devices and furniture. Exposure of the general public to phthalic anhydride may occur from the use of some of these products from which phthalic anhydride may be released.

Consumers may also be exposed to (non-synthetic) phthalic anhydride (and more than 200 other organic compounds including e.g. ketones, esters, acids, furans, pyrans, and aryl ethers) from oak smoke (Guillén and Manzanos, 2002). Oak smoke and its aqueous preparations are used in the production of several smoked foods and alcoholic beverages (*cf.* Chapter 2.2.8).

Exposure of consumers to phthalic anhydride may occur through the use of products which contain phthalic anhydride as a component in commercial preparations, e.g. Zhu, Zhang, and Shaw (1999) report that traces of phthalic anhydride were released from some hydrocarbon based wood stains for indoor materials (*cf.* Chapter 2.2.8).

Phthalic anhydride is listed in the Nordic Product Registers as a component of about 1000 preparations for industrial use. It is also listed in the Swedish and Norwegian Product Registers as being used in consumer products. In 2000, at least 96 % (31 433 tonnes of 32 648 tonnes) of the registered volume is used industrially for the manufacture of chemicals and chemical products. The major application is as an industrial intermediate and raw material, but it is also listed to be used e.g. in paints, lacquers, and varnishes, in cleaning and washing agents, as binding agent for paints and adhesives, as a construction material, and as hardener, primer, and stopping material. The main use categories are use in closed system and non-dispersive use (SPIN, 2004). Phthalic anhydride is also listed in the Swedish Product Register as a component of 98 products with a total amount of 30 526 tonnes. Most frequent uses for products are paints and varnishes, hardeners, adhesives and filling agents. The number of consumer products is 5; they contain less than 2 % of phthalic anhydride (Swedish Product Register, 2004). In the Swiss Product Register (2004) phthalic anhydride is registered for 91 products, including 30 consumer products, most of them in the categories of "paints, dyes, lacquers" and "glue, surfacer, cement, sealing mass" (Swiss Product Register, 2004).

The information from the Nordic and Swiss Product Registers are consistent with the general use categories (*cf* Chapter 2.1). It should be noted that the major use of phthalic anhydride is in the production of unsaturated polyester resins and polymers, which account for most of the applications listed in the Nordic and Swiss Product Registers. This database does not distinguish between direct uses of phthalic anhydride (as a chemical) and uses of materials, such as resins, that are produced from chemical reactions with phthalic anhydride. The commercial uses of phthalic anhydride are due to its reactivity in polymerization processes and in the formation of chemical derivatives.

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

No comprehensive toxicokinetic studies were available.

Phthalic anhydride is known to undergo rapid hydrolysis to phthalic acid upon contact with water (Andres, Grandados, and Rossi, 2001), and it is likely that a similar reaction will occur in biological systems. Therefore, phthalic acid is probably a major breakdown product of the anhydride.

Studies in Animals

In vitro Studies

No reliable studies available.

In vivo Studies

No reliable studies available.

Studies in Humans

In vitro Studies

No data available.

In vivo Studies

The excretion of phthalic anhydride in humans has been investigated in a study where urine samples were collected from nine subjects occupationally exposed to phthalic anhydride, primarily by the inhalation route. Samples were taken before, during, and after workshift. Airborne phthalic anhydride levels ranged from 0.03 to 10.5 mg/m^3 (8-hour TWA, MMAD not stated), determined from personal air samples from the worker breathing zones. Urine was also taken from a control group of 22 persons not occupational exposed to phthalic anhydride. Given that phthalic anhydride is converted to phthalic acid in the presence of water, the phthalic acid concentration in the urine was measured after esterification with methanol by electron capture gas chromatography, and expressed in terms of urinary creatinine. At low atmospheric phthalic anhydride concentrations (mean +/- SD; 0.15 +/- 0.15 mg/m^3, range 0.03 - 0.33 mg/m^3, n = 5), the excretion of phthalic acid increased from the pre-shift (7:00 hours) concentration to the post-shift (15:00 hours) concentration and decreased then until the pre-shift concentration was again reached. Exposure to higher atmospheric concentrations of phthalic anhydride (1.63 +/- 0.13 mg/m^3, n = 2; 10.5 mg/m^3, n = 1) resulted in a body load of phthalic acid which was not totally cleared overnight.. One worker exposed to high

concentration of phthalic anhydride (10.5 mg/m^3) had a pre-shift urinary concentration of 4.8 µmol of phthalic acid/mmol creatinine; approx. 14 times that of the control group. The concentration of phthalic acid in the urine was found to increase from the pre-shift level to a maximum in the immediate post-shift or evening urine sample. The concentration then decreased, and the authors estimated a half-life of approx. 14 hours without further information how this value was established. Urine samples were also subjected to acid, alkaline, and enzymatic hydrolysis by β-glucuronidase or aryl sulphatase. No evidence was seen of conjugate formation. Thus, workers occupationally exposed to atmospheric phthalic anhydride absorbed the substance with subsequent excretion in the urine as unconjugated phthalic acid (Pfaeffli, 1986).

Conclusion

On contact with water, phthalic anhydride is rapidly hydrolyzed to phthalic acid. Unconjugated phthalic acid was found in the urine of humans exposed to phthalic anhydride by the inhalation route, demonstrating systemic absorption and elimination via the urine and the existence of phthalic acid as a hydrolysis product *in vivo*.

3.1.2 Acute Toxicity

Studies in Animals

Inhalation

There are only old and insufficiently documented studies available with low number of animals and no information on purity of test compound or the methods used to generate the test atmosphere.

Dermal

There were no reliable studies available. The studies available were old with insufficient documentation for assessment.

Oral

In rats, an LD_{50} value of 1530 mg/kg bw was reported. Groups of ten Wistar rats (160 - 180 g) were dosed with 100, 500, 1000, 2000, 3100, and 5000 mg/kg bw of phthalic anhydride (purity approx. 99.8 %) dissolved in DMSO (2 ml/100 g bw). Animals were observed for 14 days but no gross pathology was reported. The symptoms observed at doses equal or higher than 500 mg/kg bw were sedation, imbalance, and bloodshot eyes. No deaths occurred in the group dosed with 100 mg/kg bw. The mortality rates were 20, 20, 40, 90, or 100 % in the 500, 1000, 2000, 3100, or 5000 mg/kg dose groups, respectively, and a LD_{50} value of 1530 mg/kg bw was calculated by using the method of Fink (Bayer AG, 1978).

Studies in Humans

Inhalation

Generalized descriptions of systemic effects with acute exposure are given in several old, poorly documented reports, which provide no reliable information on exposure levels. Headache, dizziness, nausea, epigastric burning and a feeling of suffocation were described after occupational exposure to phthalic anhydride dust or vapor (Bernard and Marchand, 1945).

Dermal

In one person occasionally exposed to phthalic anhydride by the dermal route, transient effects on the kidneys (poor function with the suppression of urinary secretion) were noted (Sagan, 1965).

Oral

No data available

Conclusion

The oral LD_{50} in rats was 1530 mg/kg bw. Clinical signs at doses equal or higher than 500 mg/kg bw included sedation, imbalance, and bloodshot eyes. There were no reliable animal acute toxicity studies available for the inhalation and dermal routes of exposure.

In poorly documented human case reports, which provide no reliable information on exposure levels, headache, dizziness, nausea, epigastric burning and a feeling of suffocation were described after acute occupational exposure to phthalic anhydride dust or vapor.

3.1.3 Irritation

Skin Irritation

Studies in Animals

Mild irritation was observed when 550 mg of 99.8 % pure phthalic anhydride flakes were applied to the shaved dorsal area of the trunk of six rabbits for 4 hours according to OECD TG 404 (no information on test substance preparation available). The dermal irritation indexes after semi-occlusive exposure were 0.83, 1.5, 1.5, and 1.0, on a scale ranging from 0 to 8 after 1, 24, 48, and 72 hours, respectively, and the average dermal irritation index was 1.21. The observed effects were reversible, since scores for all animals were zero within 5 days until the end of the experiment (Chemische Werke Huels, 1983). In another study with semi-occlusive exposure, two New Zealand white rabbits were dosed with 500 mg of solid phthalic anhydride (moistened with water, purity of test compound not given) on the ear for 24 hours and observed for 14 days. No irritant effect was observed in this study (Bayer AG, 1979).

Studies in Humans

Contact with either solid phthalic anhydride or its vapor has been reported to cause skin irritation after occupational exposure. Impurities present in the technical phthalic anhydride, naphthoquinone and maleic anhydrides, seem to contribute to these symptoms (Oettel, 1955). Following skin contact lesions ranging from erythema, blistering, ulceration and necrosis have been reported. Several authors considered that skin irritation following contact with solid material was a greater problem in summer when the skin is likely to be wet due to perspiration.

Eye Irritation

Studies in Animals

Eye irritation was reported in a study in which 50 mg of the solid compound was applied to two rabbits, respectively, and ocular irritation was scored according to Draize after 1, and 24 hours, and 2, and 7 days after application. The following maximum values were reported for phthalic anhydride (maximum values possible in the Draize scoring system are indicated in brackets for comparison). cornea 1, transitional slight cloudiness of the cornea up to day 2 (2); Iris 1 (2); conjunctiva, redness 2 (3); conjunctiva, swelling 2 (4); lacrimation 1. All effects, except conjunctiva redness (score 1 at day 7), were reversible during the seven-day observation period (Bayer AG, 1979).

Studies in Humans

Reported irritative effects on the eye after occupational exposure included conjunctivitis, lacrimation, corneal ulceration and necrosis, and photophobia. In one study workers complained of conjunctivitis when occupationally exposed to an airborne phthalic anhydride dust concentration of about 6 mg/m^3 (2 - 6 hour TWA) (Nielsen et al., 1988, 1991).

Respiratory Tract Irritation

Studies in Animals

Phthalic anhydride has not been investigated in comprehensive respiratory tract irritation studies in animals.

Studies in Humans

In humans, phthalic anhydride in the form of vapor, fumes, or dust is an irritant to mucous membranes and the upper respiratory tract. Initial exposure produces coughing, sneezing, burning sensations in the nose and throat, and increased mucous secretion. Repeated or continued exposures may result in general inflammation of the respiratory tract, nasal ulceration and bleeding, atrophy of the mucous membranes (reversible), loss of smell, hoarseness, bronchitis, urticaria, and symptoms of allergic hypersensitivity (Baader, 1955; Menschick, 1955; Frans and Pahulycz, 1993).

Conclusion

In rabbits, phthalic anhydride was slightly irritating to the skin (OECD TG 404), and irritating to the eyes. In humans, effects on the eye after occupational exposure are described (including conjunctivitis, lacrimation, corneal ulceration, necrosis, and photophobia). For humans, phthalic anhydride in the form of vapor, fumes, or dust is a primary irritant to mucous membranes and the upper respiratory tract. Initial exposure produces coughing, sneezing, burning sensations in the nose and throat, and increased mucous secretion. Repeated or continued exposures may result in general inflammation of the respiratory tract, nasal ulceration and bleeding, atrophy of the mucous membranes (reversible), loss of smell, hoarseness, bronchitis, urticaria and symptoms of allergic hypersensitivity.

3.1.4 Sensitization

Studies in Animals

Skin

The skin sensitization potential of phthalic anhydride was investigated in a guinea pig maximization test using the OECD TG 406 method without deviation. Reactions indicative of the sensitized state were seen in 90 % of treated animals, demonstrating that phthalic anhydride is a skin sensitizer (Basketter and Scholes, 1992). A murine local lymph node assay (LLNA) in accordance with the standard OECD TG 429 protocol was also conducted as part of this study. Mice were given a daily topical application of 25 µl phthalic anhydride at concentrations of 2.5, 5 or 10 % to the dorsal surface of each ear for three consecutive days. Lymphocyte proliferation far in excess of three times that of the control nodes (EC3) indicated, that phthalic anhydride was a sensitizer (Basketter and Scholes, 1992). In another LLNA, groups of mice were pretreated with 1 % sodium dodecyl sulphate (SDS) one hour before exposing the animals to 25 µl of test solution on both ears daily for three days. (The authors report that application of 1 % SDS and the test chemical generally resulted in an increased response compared to the test chemical alone). The phthalic anhydride concentrations used were 0, 0.25, 1, 2.5, 10, and 25 %. The EC3 value was determined to be 0.357 % (Van Och et al., 2000).

Respiratory Tract

The respiratory sensitizing potential of phthalic anhydride was evaluated in a guinea pig model. Two groups of 8 animals were each exposed to 0.5 or 1.0 mg/m^3 phthalic anhydride dust, three hours/day for five consecutive days; two additional groups of 16 animals each were exposed in the same manner to filtered air (control group) or 5.0 mg/m^3 phthalic anhydride dust. The mass median aerodynamic diameters (MMADs) were all in the respirable range. Two weeks after the last exposure, guinea pigs were challenged either with phthalic anhydride dust (5 mg/m^3) or with phthalic anhydride guinea pig serum albumin (PA-GPSA) conjugate dust (2.0 mg/m^3). After challenge with phthalic anhydride, the changes in respiratory rate were not significantly different from the control animals. In animals challenged with PA-GPSA conjugate one animal in the 0.5 mg/m^3 group and four animals in the 5 mg/m^3 group experienced significant and sustained increases in respiratory rate on challenge, as compared with the air control animals. The same animal in the 0.5 mg/m^3 group, one animal in the 1 mg/m^3 group, and three animals in the 5.0 mg/m^3 group experienced sustained respiratory reactions that resulted in significant increases in plethysmograph pressure, as compared with the air control animals. Linear regression analysis showed a highly significant dose-response relationship for IgG antibody levels. None of the study animals had detectable IgE antibodies to PA-GPSA. Foci were observed during histopathological examination in 8 of 8 animals in the phthalic anhydride dust-exposed and challenged group, with 3 of 8 having 189 foci or more (mean value 115; mean value control group: 1). One or two lung foci were noted in 5 of 8 filtered air control/phthalic anhydride dust-challenged guinea pigs. No indication of inflammation was noted. Alveolar hemorrhage, with accumulation of red blood cells, and a few alveolar macrophages were observed. Minimal cell hyperplasia was also noted. The authors concluded, that animals exposed to and challenged with 5.0 mg/m^3 phthalic anhydride dust had significant numbers of hemorrhagic lung foci. Those animals with the greatest number of foci had high IgG antibody activity to phthalic anhydride (Sarlo et al., 1994).

Studies in Humans

There is evidence to suggest that respiratory and skin sensitization can occur as a consequence of occupational exposure to phthalic anhydride. Evaluation of the available human data is hampered because most studies were conducted in factories where epoxy resins were handled and occupational exposure to several anhydrides, including phthalic anhydride and e.g. maleic anhydride occurred. Bernstein *et al*. demonstrated that workers with occupational asthma after exposure to acid anhydride compounds showed specific- and cross-reactive IgE antibody response (Bernstein *et al*., 1984). Additionally, impurities present in the technical phthalic anhydride, e.g. naphthoquinone and maleic anhydrides, seem to contribute to the sensitizing potential (Oettel, 1955).

Skin

Two cases of urticarical rashes on exposed areas of the skin were found among workers at a chemical plant handling phthalic anhydride (Menschick, 1955)

191 workers were patch tested with the resin and hardeners, including phthalic anhydride at a plastics factory where epoxy resins, including maleic anhydride and phthalic anhydride, were processed. An allergic response to a 0.1 % solution of phthalic anhydride in acetone was observed in 14 % of the workers (Woyton et al., 1976).

Respiratory Tract

Phthalic anhydride has been known as a respiratory sensitizer since 1939 when the first case of asthma and allergic rhinitis was reported to be due to sensitivity to phthalic anhydride (Kern, 1939).

Phthalic anhydride sensitization may also be associated with an asthma-rhinitis-conjunctivitis syndrome or with a delayed reaction and influenza-like symptoms.

Among 118 workers occasionally exposed to phthalic anhydride dust for 2 months or more, 28 (24 %) suffered from work-related rhinitis, 13 (11 %) from chronic productive bronchitis, and 21 (28 %) from work-associated asthma. Three out of eleven asthmatics had a phthalic anhydride-positive skin test, and in two subjects the presence of antibodies was demonstrated. The average concentration of phthalic anhydride dust at the workplaces was given as 3–13 mg/m^3, of which 40-46 % was in the inspirable dust fraction (Wernfors et al., 1986).

In a study of two plants producing resin the time-weighted average (TWA) air level during loading of phthalic anhydride was 6.6 (1.5 - 17.4) mg/m^3. Maleic anhydride, trimellitic anhydride, and isophthalic anhydride were also used in the plants, but "to a much lower degree". A control group of 22 workers from a food processing factory, matched for age and smoking habits, was used for comparison throughout the study. In 60 workers (mean age 44 years; average exposure approximately 12 years), symptoms of rhinitis and/or conjunctivitis were frequently reported, mostly by the most heavily exposed workers (69 %). Five workers (14 %), all heavily exposed during some periods, exhibited a phthalic anhydride-associated bronchial asthma. Asthma reactions possibly correlate with specific serum IgG antibody levels, but do not appear to relate to IgE or IgM levels. The authors reported that the clinical symptoms seemed to appear after repeated peak exposure to phthalic anhydride concentrations of about 6 mg/m^3. In more than one third of the workers exposed to such concentrations increased levels of specific IgG directed against phthalic anhydride were found (Nielsen et al., 1988).

A group of 23 men (mean age 35 years; average exposure for 7 years) regularly exposed to phthalic anhydride during reactor loading activities while employed in polyester resin factories was investigated. A TWA air level during loading of 6.6 mg/m^3 was reported. A control group of 18 men employed in a municipal engineering department, matched for age and smoking habits, served as controls. As in the previous study, maleic anhydride, trimellitic anhydride, and isophthalic anhydride were also used in the plants, but "to a much lower degree" than phthalic anhydride (TWA 0.6 mg/m^3 for maleic anhydride). Work-related respiratory symptoms were more prevalent in exposed subjects compared to control subjects (eyes 48 % vs 6 %, nose, 39 % vs 0 %), but the control group exhibited more symptoms of nonspecific bronchial hyperreactivity (44 % vs 13 %). Two exposed subjects had work-related asthma. The exposed group had significantly higher total serum IgE levels, although phthalic anhydride-specific IgE levels were similar for both groups. Specific IgG levels were, as observed in the previous study, significantly greater in the exposed group. Lung function tests did not show any difference between the two groups (Nielsen et al., 1991).

Conclusion

Phthalic anhydride demonstrated skin sensitizing properties in animals, with positive results being observed in guinea pig tests according to OECD TG 406 and in local lymph node assays similar to OECD TG 429. Evidence that phthalic anhydride has respiratory sensitization potential has been demonstrated in an experimental guinea pig model. In humans, there are a number of reports providing information on the respiratory sensitization potential of phthalic anhydride after occupational exposure. Workers were reported to suffer from work-related rhinitis, chronic productive bronchitis, and work-associated asthma. Phthalic anhydride sensitization is generally associated with either an asthma-rhinitis-conjunctivitis syndrome or with a delayed reaction and influenza-like symptoms and with increased IgG and/or phthalic anhydride specific IgE levels in the blood. Reports on skin reactions in humans are rare.

3.1.5 Repeated Dose Toxicity

Repeated dose toxicity was investigated in 7-week-studies and in long-term (carcinogenicity) studies in rats and mice, using the oral route of exposure. There are no human data available on repeated dose toxicity.

Studies in Animals

Inhalation

There are no valid data available. The available studies are old with insufficient documentation and low number of animals. No information was available, for instance, on the purity of the test substance or the methods used to generate the test atmosphere.

Dermal

No data are available.

Oral

Briefly reported 7-week repeated dose studies were conducted in Fischer 344 rats and B6C3F1 mice, to provide the basis for the choice of dose levels for more extensively documented carcinogenicity studies. Groups of five animals of each sex were exposed to phthalic anhydride via the diet at levels of 0, 6200, 12 500, 25 000, and 50,000 ppm (approximate doses in rats: 0, 410, 830, 1660, and 3330 mg/kg bw/day; mice: 0, 890, 1790, 3570, and 7140 mg/kg bw/day). Body weights were recorded throughout the study and unspecified tissues were examined microscopically. In rats, there was a significant reduction in body-weight gain (approximately 75 % weight gain compared to controls at seven weeks) at the highest dose level (50 000 ppm). At 25 000 ppm, centrilobular cytoplasmic vacuolation were seen in the livers of four male rats; although tissues were essentially normal in all rats at 50 000 ppm. In mice no effect on body weight was observed at any dose, and there were no microscopic abnormalities in any mice at all dose levels (NCI, 1979).

In a rat chronic feeding study, groups of 50 Fischer 344 rats per sex were exposed to 7500 or 15 000 ppm (approximately 500 and 1000 mg/kg bw/day) of phthalic anhydride in the diet. The control group consisted of 20 animals per sex. At termination, after 105 weeks, all major organs were subjected to both macroscopic and microscopic examination. Apart from a < 10 % reduction in the bodyweight gain of the high dose males, there were no treatment-related differences in mortality or microscopic changes among the groups. The survival rate was not different between the groups and was generally ≥ 70 %. No hematology and no clinical chemistry endpoints were examined (NCI, 1979).

In a mouse chronic feeding study, groups of 20 control or 50 treated B6C3F1 mice of each sex were exposed via the diet at levels of 0, 25 000, or 50 000 ppm for the first 32 weeks of a 104 week treatment period (approximately 3570 or 7140 mg/kg bw/day). Because of excessive body weight loss during the first 32 weeks the exposure levels in males were reduced to 12 500 or 25 000 ppm (approximately 1785 or 3570 mg/kg bw/day), respectively, and the doses for the females were reduced to 6250 and 12 500 ppm (approximately 890 or 1780 mg/kg bw/day), respectively, for the remainder of the study. The time-weighted average doses for the males were either 16 346 or 32 692 ppm (approximately 2340 or 4670 mg/kg bw/day), and those for the females were either 12 019 or 24 038 ppm (approximately 1717 or 3430 mg/kg bw/day). In the treated groups a dose-related reduction in bodyweight gain was observed throughout the study with terminal bodyweights reduced by 12 and 27 % compared to controls for the low and high dose groups, respectively. The survival rate at the end of the treatment period was at least 74 % in all groups. The NCI (1979) concluded that there were no treatment-related non-neoplastic pathological effects in the mice. Re-examination of the incidence data by the US EPA, Integrated Risk Information System (IRIS)

showed significantly increased incidences of lung and kidney lymphocytosis in the low- and high-dose males and females (incidence in controls, low-dose, and high-dose groups; males' lung: 30 %, 38 %, and 61 %, females' lung: 10 %, 65 %, 71 %, males' kidney: 0 %, 30 %, and 76 %, females' kidney: 0%, 46 %, 54 %), chronic bile duct inflammation in the high-dose males (5 %, 14 %, 35 %), and females (50 %, 63 %, and 75 %), and dose-related adrenal atrophy (0 %, 47 %, 83 %) and mineralization of the thalamus in the low-\and high-dose males (0 %, 36 %, 23 %). No historical control data on the incidences of these findings in the testing laboratory were available, and the biological significance of these findings is therefore difficult to ascertain. Nevertheless, based on this re-evaluation, the time weighted LOAEL was set to be 12,019 ppm level in female mice (approximately 1717 mg/kg bw/day) and 16 346 ppm in male mice (approximately 2340 mg/kg bw/day); no NOAEL was obtained in this study (NCI, 1979; EPA, 1992).

Conclusion

Phthalic anhydride has been shown to have low repeated dose toxicity by the oral route in rats. The evidence of toxicity in a chronic rat study is limited to adverse effects on body-weight gain at the dose level of 1000 mg/kg bw/day. The NOAEL was at 500 mg/kg bw/day. It is noted that no hematology and clinical biochemistry examinations were performed in this study. A NOAEL could not be established in a chronic feeding study in mice because of pathological effects seen down to the lowest tested dose level (LOAELs: 12 019 ppm level in female mice = approximately 1717 mg/kg bw/day, and 16 346 ppm in male mice = approximately 2340 mg/kg bw/day; increased incidences of lung and kidney lymphocytosis in the males and females, and dose-related adrenal atrophy and mineralization of the thalamus in males. The LOAELs are time-weighted averages because a dose reduction in males from 25 000 to 12 500 ppm (= approximately 1785 mg/kg bw/day) and for females from 12 500 to 6250 ppm (= approximately 890 mg/kg bw/day) was necessary after 32 weeks of exposure due to reduced weight gains). There were no valid repeated dose studies available using the dermal or respiratory routes of exposure.

3.1.6 Mutagenicity

Several *in vitro* bacterial mutation assays are available which were conducted similarly to current guidelines. *In vitro* chromosome aberrations were investigated in two studies. There are no *in vivo* data on mutagenicity available.

In vitro Studies

Several bacterial mutation assays have been conducted and demonstrated no mutagenic activity. The most recent studies were conducted by a protocol similar to OECD TG 471. In one study the pre-incubation procedure was performed with *Salmonella typhimurium* TA 100, TA 1535, TA 98, TA 1537, and *Escherichia coli* WP2uvrA at concentrations up to 5000 µg/plate. Cytotoxic effects were observed in the absence and in the presence of a metabolic activator (Aroclor 1254-induced rat liver S9) at concentrations equal or higher than 313 µg/plate. Phthalic anhydride did not induce mutations in the bacterial mutation test in either the absence or presence of metabolic activator in any strain tested. The positive and negative controls included in the experiment showed the expected results (JETOC, 1996). In another study four *S. typhimurium* strains (TA 98, TA 100, TA 1535, TA 1537) were exposed to phthalic anhydride in a pre-incubation assay. Concentrations up to 3333 µg/plate were used with metabolic activator (rat- and hamster-liver S9) in all four strains and 333 µg/plate (TA 100, TA 1535, TA 1537) or 1000 µg/plate (TA 98) in its absence. Phthalic anhydride did not induce mutations in this study. Positive and solvent controls (DMSO) gave the expected results (Zeiger et al., 1985).

The ability of phthalic anhydride to induce chromosome aberrations was investigated in two studies. Chinese hamster ovary cells were exposed to 30 - 300 µg/ml (approximately 0.2 - 2 mM) with or

without S9; the highest concentration was selected as a cytotoxic level on the basis of a preliminary study. Cells were exposed to phthalic anhydride for 2 hours in the presence of metabolic activation (S9), and further incubated for 8-12 hours. In the tests without metabolic activation, the cells were exposed to phthalic anhydride throughout the incubation period. No dose-related increases in aberrations were observed. The low number of evaluated metaphases (100), and the lack of an independent repeat are limitations of this study, resulting in a low sensitivity of the test (Galloway *et al.,* 1987). In a second study by the same group, Chinese hamster ovary cells were exposed to higher doses (6, 8, 10 mM) for 3 hours in the presence or absence of S9. Cells were then washed, further incubated and harvested at 20 hours from the beginning of the treatment. Phthalic anhydride caused a decrease in pH when added to culture medium and was immediately neutralized with NaOH. Effects were observed in the main study only without S9 and only at the highest compound concentration which was very toxic (remaining cell counts 29 %) and gave precipitate. Chromosome aberration rate increased to 18.5 % at the highest dose compared with a control of 3 %. Only a small, not statistically significant, increase in aberrations was observed at a slightly lower concentration (8 mM compared to 10 mM) which showed lower cytotoxicity (remaining cell counts 54 %) and no precipitate. It is noted that the negative control values in the phthalic anhydride experiment (3 %) were out of the usual control values described in the publication (0.00 - 2.25%, mean value 1.5 %) and limited documentation hampers the evaluation of this information There was no statistically significant increase in aberrations with and without S9 activation in a pre-experiment at 10 mM phthalic anhydride (Hilliard et al., 1998). The genotoxic effect found with phthalic anhydride *in vitro* at extremely high, cytotoxic concentrations, and only in the absence of a metabolic activation system is not expected to be relevant under *in vivo* conditions, where phthalic anhydride is rapidly hydrolyzed to the non-genotoxic phthalic acid. [The data on phthalic acid have recently been reviewed and published by the German Research Foundation (DFG, 2006).]

A sister chromatid exchange (SCE) test was conducted using Chinese hamster ovary cells in an apparently well-conducted, but briefly-reported study. Cells were exposed to 10 - 300 µg/ml with or without S9; the highest concentration was selected as a cytotoxic level on the basis of a preliminary study. Cells were exposed for 8 to 12 hours without S9 or for 2 hours in the presence of S9. One hundred cells per dose level were evaluated. No significant increase in sister chromatid exchanges was observed at any concentration investigated (Galloway et al., 1987).

In vivo Studies

No data available.

Conclusion

Phthalic anhydride was not mutagenic in the Ames test with and without metabolic activation (OECD TG 471). Chromosomal aberrations were induced in mammalian cells *in vitro* at the highest phthalic anhydride concentrations (10 mM) only in the absence of S9 mix with concomitant marked cytotoxicity and compound precipitate. *In vivo* studies are not available. Overall, it can be concluded that phthalic anhydride is genotoxic *in vitro* at extremely high, cytotoxic concentrations, and only in the absence of a metabolic activation system. This genotoxic effect is not expected to be relevant under *in vivo* conditions, where phthalic anhydride is rapidly hydrolyzed to the non-genotoxic phthalic acid.

3.1.7 Carcinogenicity

Two oral carcinogenicity studies in rats and mice are available which were conducted similarly to current guidelines. No human epidemiology data is available.

In vitro Studies

No valid studies are available

In vivo Studies in Animals

Inhalation

No studies are available

Dermal

No studies are available

Oral

Carcinogenicity studies have been conducted in rats and mice. Groups of 20 control and 50 treated Fischer 344 rats per sex were exposed via the diet at levels of 0, 7500, or 15 000 ppm (0, approx. 500 or 1000 mg/kg bw/day) for 105 weeks. The survival rate at the end of the treatment period was at least 70 % in all groups. There were no significant non-neoplastic abnormalities, and adverse effects were limited to decreased body-weight gain at dose levels of 1000 mg/kg bw/day (i.e., < 10 % relative to control). The survival rate was not different between the groups and was generally ≥ 70 % (see also Chapter 3.1.5. on repeated dose toxicity). No difference was observed between the dosed and control groups in frequency or distribution of neoplasms, except for malignant lymphoma in the female rats. The incidence of malignant lymphoma in the control females was 1/20, in the low-dose females 11/50, and in the high dose females 4/50. Due to the high and fluctuating incidence of this type of malignant lymphoma commonly observed in control F344 rats, the apparent difference in incidences of the tumor in the dosed and control groups were not considered to be compound related (NCI, 1979).

For the mice (B6C3F strain), groups of identical size were exposed via the diet at level of 0, 25 000, or 50 000 ppm for the first 32 weeks of a 104 weeks treatment period. Because of excessive body-weight loss the exposure levels in males were reduced to 12 500 or 25 000 ppm, respectively, and the doses for the females were reduced to 6250 and 12 500 ppm, respectively, for the remainder of the study. The time-weighted average doses for the males were either 16 346 or 32 692 ppm (approximately 2340 or 4670 mg/kg bw/day), and those for the females were either 12 019 or 24 038 ppm (approximately 1717 or 3430 mg/kg bw/day). Non-neoplastic effects observed at all doses included increased incidences of lung and kidney lymphocytosis, adrenal atrophy and mineralization of the thalamus. There was no difference in mortality among the groups, and the survival rates at the end of the treatment period were at least 74 % in all groups (see also Chapter 3.1.5. on repeated dose toxicity). No neoplastic changes that were considered to be treatment-related were observed in the mice. Therefore no evidence of carcinogenicity was seen in either species (NCI, 1979).

Conclusion

No evidence of carcinogenicity was seen in rats after exposure to approximately 1000 mg/kg bw/day of phthalic anhydride, or in male and female mice after exposure to 4670, and 3430 mg/kg bw/day, respectively, in comprehensive chronic (105-week) feeding studies.

3.1.8 Toxicity for Reproduction

Studies in Animals

Effects on Fertility

No fertility studies with phthalic anhydride are available. No effects on reproductive organs were observed in the previously described oral carcinogenicity study in rats and mice. The pathologic evaluation consisted of gross and microscopic examination of reproductive organs; in male rats, preputial gland, prostate, seminal vesicle, testis and epididymis, and the mammary gland; in female rats, mammary gland, uterus, endothelial gland, and ovary; in male mice epididymis; in female mice uterus and ovary. No treatment-related changes were observed for any reproductive organ investigated during macroscopic and microscopic examination of all major organs (NOAEL, rat: 1000 mg/kg bw/day; NOAEL, mouse (time-weighted average): 3430 (f), 4670 (m) mg/kg bw/day). (NCI, 1979).

Decreased sperm motility was reported in one study in which male rats were exposed via inhalation (Protsenko, 1970) at 0.2 mg/m^3 and no effects were observed at 0.02 mg/m^3. The small sample size of 6 animals per group, poor documentation, and lack of data on the biological and statistical relevance of the observed effects limit however the confidence in these study results substantially.

Developmental Toxicity

No valid studies are available investigating the effects of phthalic anhydride on toxicity for reproduction. In a non-guideline study, phthalic anhydride was reported to be a developmental toxicant in mice following intraperitoneal injection of doses in the adult lethal range. In this study (Fabro, Shull, and Brown, 1982), pregnant CD-1 mice (10/dose group) were injected intraperitoneally with phthalic anhydride in 0.5 % carboxymethyl cellulose solution on gestational days 8 - 10. In the publication it was stated that dosing was started at the 95 % confidence limit of the LD_{01} and progressing geometrically downward until no effect was observed. Animals were terminated on day 18 and examined for fetal viability and number, resorptions, and gross malformations. The LD_{01} and LD_{50} values for adult lethality were investigated in an independent experiment with non-pregnant mice and reported to be 0.37 mmol/kg bw/day (95 % confidence limit 0.19 - 0.43 mmol/kg bw/day) and 0.51 mmol/kg bw/day (0.44 - 0.57 mmol/kg bw/day), respectively. The tD_{05} and tD_{50} values for teratogenicity (grossly observable malformations and fetal internal malformations) were extrapolated to be 0.4 mmol/kg bw/day (no 95 % confidence limit could be calculated) and 1.37 mmol/kg bw/day (no 95 % confidence limit could be calculated), respectively. The reliability of this study is limited because of the very poor documentation, e.g. no data on the precise dose levels and number of doses investigated, no data on positive or negative controls, and only extrapolated LD_{01}, LD_{50}, tD_{05}, and tD_{50} data given without any further information. The teratogenic effects (tD_{05} 0.4 mmol/kg bw/day) were observed at doses were maternal lethality (LD_{01} 0.37 mmol/kg bw/day) occurred. The statistical relevance of the extrapolated values can be questioned because of the "very shallow" dose-response curve mentioned in the publication and the lack of 95 % confidence limits in the phthalic anhydride experiments. Intraperitoneal injection is not a relevant route of human exposure in particular if the compound demonstrated an irritant potential because observed effects might be due to local irritation at the site of injection, the peritoneal cavity. Additionally, this route is also not relevant for chemicals with low chemical stability in aqueous solutions, because after exposure by the oral, dermal or inhalation route the parent compound will not reach the reproductive organs.

Phthalic anhydride is known to undergo rapid hydrolysis to phthalic acid on contact with water (Andres, Grandados, and Rossi, 2001). It is likely that a similar reaction will occur in biological systems, which is supported by the presence of unconjugated phthalic acid in the urine of workers occupationally exposed to phthalic anhydride (Pfaeffli, 1986).

The developmental toxicity of phthalic acid was investigated in a developmental toxicity study. Groups of eleven pregnant Wistar rats were fed a diet containing phthalic acid at a dose of 0, 1.25, 2.5, or 5.0 % ad libitum on GD 7 – GD 16 (approximately 0, 1000, 1700, 3000 mg/kg bw/day). The administration in the feed was selected because of only slight solubility of phthalic acid in water and oil. The pregnant rats were observed daily for evidence of clinical signs of toxicity, maternal body weight and food consumption. Average daily intake of phthalic acid was calculated. The pregnant rats were sacrificed on day 20 of pregnancy. The peritoneal cavity and uterus were opened and the numbers of live and dead fetuses and resorptions were counted. The gravid uterus was removed and the rats weighed again. The adjusted weight gain, i.e. maternal weight gain throughout pregnancy corrected for gravid uterine weight, was calculated. The live fetuses removed from the uterus were sexed, weighed and inspected for external malformations and malformations within the oral cavity. Approximately two-thirds of live fetuses in each litter, randomly selected, were stained with alizarin red S and examined for skeletal malformations. The remaining live fetuses in each litter were fixed in Bouin's solution and examined for internal malformations. Maternal toxicity occurred in the 2.5 and 5.0 % groups as demonstrated by decreases in the adjusted maternal body-weight gain (maternal bw gain excluding the gravid uterus; 30, 42, or 50 g for the 5, 2.5, or control group, respectively) during the administration period. No significant changes in maternal parameters were found in the 1.25 % group (adjusted body weight gain 47 g). No deaths or clinical signs of toxicity were noted in any group. No significant changes induced by phthalic acid were detected in the incidence of postimplantation loss, number and sex ratio of live fetuses. Significant decreases in the weight of male fetuses and decreased numbers of ossified centers of the caudal vertebrae were found only in the 5.0 % group, where significant maternal toxicity also was observed. Morphological examinations of fetuses revealed no evidence of developmental toxicity (NOAEL, maternal toxicity: 1.25 % in feed = approximately 1000 mg/kg bw/day; NOAEL, developmental toxicity: 2.5 % in feed = approximately 1700 mg/kg bw/day). (Ema et al., 1997).

Conclusion:

There was no fertility study with phthalic anhydride available. No evidence of toxicity to reproductive organs was observed in comprehensive carcinogenicity studies in rats and mice, as no treatment-related changes were observed for any reproductive organ investigated during macroscopic and microscopic examination (NOAEL, rat: 1000 mg/kg bw/day; NOAEL, mouse (time-weighted average): 3430 (f), 4670 (m) mg/kg bw/day). Following i.p. injection, an exposure route which is of unknown relevance for the normal human situation, of doses in the lethal range, developmental toxicity was found in mice in a poorly reported study. However, the chemical is quickly hydrolyzed to phthalic acid after oral, dermal or inhalation exposure. Phthalic acid was investigated in a developmental toxicity feeding study in rats and gave no evidence of embryotoxicity, or fetotoxicity at a non-maternally toxic dose level (1.25 % in feed = approximately 1000 mg/kg bw/day = NOAEL for maternal toxicity). Significant decreases in the weight of male fetuses and in the numbers of ossified centers of the caudal vertebrae were, however, found in the 5.0 % group, where maternal toxicity was also observed (NOAEL, developmental toxicity: 2.5 % in feed = approximately 1700 mg/kg bw/day). Based on the data of phthalic acid, the hydrolysis product of phthalic anhydride, it is concluded that, in the absence of maternal toxicity, phthalic anhydride is not a developmental toxicant.

3.2 Initial Assessment for Human Health

On contact with water, phthalic anhydride is rapidly hydrolyzed to phthalic acid. Unconjugated phthalic acid was found in the urine of humans exposed to phthalic anhydride by the inhalation route, demonstrating systemic absorption and elimination via the urine and the existence of phthalic acid as a hydrolysis product *in vivo*.

The oral LD_{50} in rats was 1530 mg/kg bw. Clinical signs at doses equal or higher than 500 mg/kg bw included sedation, imbalance, and bloodshot eyes. There were no reliable animal acute toxicity studies available for the inhalation and dermal routes of exposure.

In poorly documented human case reports, which provide no reliable information on exposure levels, headache, dizziness, nausea, epigastric burning and a feeling of suffocation were described after acute occupational exposure to phthalic anhydride dust or vapor.

In rabbits, phthalic anhydride was slightly irritating to the skin (OECD TG 404), and irritating to the eyes. In humans, effects on the eye after occupational exposure are described (including conjunctivitis, lacrimation, corneal ulceration, necrosis, and photophobia). For humans, phthalic anhydride in the form of vapor, fumes, or dust is a primary irritant to mucous membranes and the upper respiratory tract. Initial exposure produces coughing, sneezing, burning sensations in the nose and throat, and increased mucous secretion. Repeated or continued exposures may result in general inflammation of the respiratory tract, nasal ulceration and bleeding, atrophy of the mucous membranes (reversible), loss of smell, hoarseness, bronchitis, urticaria and symptoms of allergic hypersensitivity.

Phthalic anhydride demonstrated skin sensitizing properties in animals, with positive results being observed in guinea pig tests according to OECD TG 406 and in local lymph node assays similar to OECD TG 429. Evidence that phthalic anhydride has respiratory sensitization potential has been demonstrated in an experimental guinea pig model. In humans, there are a number of reports providing information on the respiratory sensitization potential of phthalic anhydride after occupational exposure. Workers were reported to suffer from work-related rhinitis, chronic productive bronchitis, and work-associated asthma. Phthalic anhydride sensitization is generally associated with either an asthma-rhinitis-conjunctivitis syndrome or with a delayed reaction and influenza-like symptoms and with increased IgG and/or phthalic anhydride specific IgE levels in the blood. Reports on skin reactions in humans are rare.

Phthalic anhydride has been shown to have low repeated dose toxicity by the oral route in rats. The evidence of toxicity in a chronic rat study is limited to adverse effects on body-weight gain at the dose level of 1000 mg/kg bw/day. The NOAEL was at 500 mg/kg bw/day. It is noted that no hematology and clinical biochemistry examinations were performed in this study. A NOAEL could not be established in a chronic feeding study in mice because of pathological effects seen down to the lowest tested dose level (LOAELs: 12 019 ppm level in female mice = approximately 1717 mg/kg bw/day, and 16 346 ppm in male mice = approximately 2340 mg/kg bw/day; increased incidences of lung and kidney lymphocytosis in the males and females, and dose-related adrenal atrophy and mineralization of the thalamus in males. The LOAELs are time-weighted averages because a dose reduction in males from 25 000 to 12 500 ppm (= approximately 1785 mg/kg bw/day) and for females from 12 500 to 6250 ppm (= approximately 890 mg/kg bw/day) was necessary after 32 weeks of exposure due to reduced weight gains). There were no valid repeated dose studies available using the dermal or respiratory routes of exposure.

Phthalic anhydride was not mutagenic in the Ames test with and without metabolic activation (OECD TG 471). Chromosomal aberrations were induced in mammalian cells *in vitro* at the highest phthalic anhydride concentrations (10 mM) only in the absence of S9 mix with concomitant marked cytotoxicity and compound precipitate. *In vivo* studies are not available. Overall, it can be concluded that phthalic anhydride is genotoxic *in vitro* at extremely high, cytotoxic concentrations, and only in the absence of a metabolic activation system. This genotoxic effect is not expected to be relevant under *in vivo* conditions, where phthalic anhydride is rapidly hydrolyzed to the non-genotoxic phthalic acid.

No evidence of carcinogenicity was seen in rats after exposure to approximately 1000 mg/kg bw/day of phthalic anhydride, or in male and female mice after exposure to 4670, and 3430 mg/kg bw/day, respectively, in comprehensive chronic (105-week) feeding studies.

There was no fertility study with phthalic anhydride available. No evidence of toxicity to reproductive organs was observed in comprehensive carcinogenicity studies in rats and mice, as no treatment-related changes were observed for any reproductive organ investigated during macroscopic and microscopic examination (NOAEL, rat: 1000 mg/kg bw/day; NOAEL (time-weighted average) mouse: 3430 (f), 4670 (m) mg/kg bw/day). Following i.p. injection, an exposure route which is of unknown relevance for the normal human situation, of doses in the lethal range, developmental toxicity was found in mice in a poorly reported study. However, the chemical is quickly hydrolysed to phthalic acid after oral, dermal or inhalation exposure. Phthalic acid was investigated in a developmental toxicity feeding study in rats and gave no evidence of embryotoxicity, or fetotoxicity at a non-maternally toxic dose level (1.25 % in feed = approximately 1000 mg/kg bw/day = NOAEL for maternal toxicity). Significant decreases in the weight of male fetuses and in the numbers of ossified centers of the caudal vertebrae were, however, found in the 5.0 % group, where maternal toxicity was also observed (NOAEL, developmental toxicity: 2.5 % in feed = approximately 1700 mg/kg bw/day). Based on the data of phthalic acid, the hydrolysis product of phthalic anhydride, it is concluded that, in the absence of maternal toxicity, phthalic anhydride is not a developmental toxicant.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Phthalic anhydride reacts rapidly with water, forming phthalic acid. Since the half-life of phthalic anhydride in water is in the range of seconds to minutes at neutral pH, virtually all phthalic anhydride is converted to phthalic acid during the usual preparation (stirring) periods of test substance solutions according to OECD TG. Thus, tests with phthalic anhydride in aquatic solutions measure effects of phthalic acid rather than phthalic anhydride. Consequently, also phthalic acid can be used as the test substance to evaluate the aquatic effects of phthalic anhydride (Table 10).

Acute Toxicity Test Results

Prolonged toxicity of phthalic anhydride to fish (*Danio rerio*) has been tested under semistatic conditions in accordance to OECD Guideline Draft "Early Life Stage. A 7 d-LC_{50} of 560 mg/l was measured (van Leeuwen, Grootelaar and Niebeek, 1990). In an acute test with phthalic acid performed with *Cyprinus carpio* under semistatic conditions a 48 h-LC_{50} of > 500 mg/l was obtained (Zhao et al., 1996).

Concerning the toxicity with *Daphnia magna* there are tests available with phthalic acid. A test on the acute toxicity to *Daphnia magna* was performed according to “Methods for Acute Toxicity Tests” with fish, macroinvertebrates and amphibians of the US EPA. For a test period of 48 hours an EC_{50} value of > 640 mg/l was obtained (Adams and Renaudette, 1986). Another test with *Daphnia magna* resulted in a 24 h-EC_{50} of 140 mg/l (Sepic, Bricelj, and Leskovsek, 2003). One more test on the acute toxicity of phthalic acid to the invertebrate *Daphnia magna* was performed in a static test system. For a test period of 24 hours an EC_{50} value of 4,900 mg/l was reported (Zhao et al., 1996). With the aquatic crustacean *Thamnocephalus platyurus*, a 24 h-EC_{50} of 220 mg/l for phthalic acid was obtained (Sepic, Bricelj, and Leskovsek, 2003).

Algal toxicity was determined by a GLP test with *Desmodesmus subspicatus* in the presence of phthalic acid. Two limit tests were conducted with each 100 mg/l with and without pH adjustment. The stability of the test substance was experimentally determined via HPLC before and after an exposure of 72 hours. The 72 h-EC_0 was ≥ 100 mg/l according to the OECD TG 201 “Algal Growth Inhibition Test”; the recovery rate was > 98 %, therefore the nominal value was reported. The

results are related to both endpoints growth rate and biomass. Without pH adjustment at 100 mg/l 100 % inhibition was observed after 72 hours; pH was determined to be in the range of 4.9 to 5.1. This indicates that phthalic acid causes a pH shift in algal medium. It is the resulting pH that determines the impact of phthalic acid on algae as shown with buffered test substance solution. Thus, toxic effects are not due to substance inherent properties but to a function of the pH (Bayer Industry Services, 2004c).

One test with the toad *Bufo bufo japonicus* is available. The toxicity of phthalic acid towards the tadpoles of this toad was tested under several pH conditions and at 25 °C. Applied concentrations were 13, 18, 23, 32, 40, and 42 mg/l. After 24 hours, no toxicity was observed at any of the concentrations tested. Furthermore the pH of the test system had no influence on the test result between pH 6 to pH 10. This value is assumed to be nominal, as no analytical monitoring is mentioned (Nishiuchi, 1980).

In a static acute toxicity test towards phthalic acid with larvae of *Chironomus plumosus* an effective concentration (48 h-EC_{50}) concerning the endpoint immobilisation of greater than 72 mg/l was measured (Streufert, Jones, and Sanders, 1980).

Chronic Toxicity Test Results

Chronic toxicity data of phthalic anhydride to fish are available. The test was performed with *Oncorhynchus mykiss* (*Salmo gairdneri*) according to the OECD Guideline Draft "Early Life Stage". After 60 days an effective LOEC of 32 mg/l was determined. Geometric series of 7 test concentrations using a factor of 3.2 was used. With a factor of 3.2 the next lowest concentration is 10 mg/l which corresponds to the no effect concentration (NOEC) of 10 mg/l. Not only mortality but also other endpoints like total embryotoxicity were tested (Van Leeuwen, Grootelaar, and Niebeek, 1990).

Chronic toxicity of phthalic acid to algae was tested according to OECD TG 201. For *Desmodesmus subspicatus* the 72 h-EC_0 (= NOEC) is ≥ 100 mg/l in pH adjusted medium (Bayer Industry Services, 2004c).

There are no results available on chronic toxicity to *daphnids*.

Table 11 Toxicity of phthalic anhydride and phthalic acid to **aquatic** organisms

Test substance	Species	Test type	Parameter	Effect concentration (nominal)	Reference	IUCLID
Phthalic anhydride	*Danio rerio*	Semistatic	7 d-LC_{50}, buffered*	560 mg/l	Van Leeuwen, Grootelaar, and Niebeek, 1990	4.1
Phthalic acid	*Cyprinus carpio*	Semistatic	48 h-LC_{50}, buffered	> 500 mg/l	Zhao et al., 1996	4.1
Phthalic anhydride	*Oncorhynchus mykiss*	Semistatic	60 d-$LC_{50\ mortality}$ 60 d-$LOEC_{length}$ 60 d-NOEC, buffered*	44.2 mg/l 32 mg/l 10 mg/l	Van Leeuwen, Grootelaar, and Niebeek, 1990	4.5.1
Phthalic acid	*Daphnia magna*	Static	48 h-EC_{50}, buffered	> 640 mg/l	Adams and Renaudette, 1986	4.2
Phthalic acid	*Daphnia magna*	Static	24 h-$EC_{50,}$ buffered	140 mg/l	Sepic, Bricelj, and Leskovsek, 2003	4.2
Phthalic acid	*Daphnia magna*	Static	24 h-EC_{50}, buffered	4900 mg/l	Zhao et al., 1996	4.2
Phthalic acid	*Thamnocephalus platyurus*	Static	24 h-$EC_{50,}$ buffered	220 mg/l	Sepic, Bricelj, and Leskovsek, 2003	4.2
Phthalic acid	*Desmodesmus subspicatus*	Static	72 h-EC_{50} and $NOEC_{\text{growth rate and biomass}}$, buffered 72 h-$EC_{100\ \text{growth rate and biomass}}$, unbuffered	≥ 100 mg/l ≤ 100 mg/l	Bayer Industry Services, 2004c	4.3
Phthalic acid	*Bufo bufo japonicus* (amphibian)	Static	24 h-$LC_{0\ \text{mortality of the tadpole}}$, buffered to pH 6-10	> 42 mg/l	Nishiuchi, 1980	4.1
Phthalic acid	*Chironomus plumosus* (insect larvae)	Static	48 h-$EC_{50\ \text{Immobilisation}}$, buffered*	> 72 mg/l	Streufert, Jones and Sanders, 1980	4.2

*no information is given on using a buffered medium, but pH value of the test medium indicates a pH adjustment

Determination of $PNEC_{aqua}$

Since chronic toxicity tests are available for fish and algae with phthalic anhydride and phthalic acid, respectively, an assessment factor of 50 can be applied using the lowest available effect concentration (NOEC = 10 mg/l) which was obtained for *Oncorhynchus mykiss* (*Salmo gairdneri*). Thus, the $PNEC_{aqua}$ was calculated to

$PNEC_{aqua}$ = 200 µg/l.

Toxicity to Microorganisms

Toxicity of phthalic anhydride to activated sludge was evaluated by Bayer AG (1984) according to the ISO 8192. The activated sludge obtained an EC_{50} value of > 1000 mg/l when exposed to phthalic anhydride for 3 hours at a pH between 7.4 and 7.6.

The toxicity of phthalic acid to *Pseusomonas putida* was tested in a 16 hours test with pH adjustment to 7.4. The population growth impairment was used as endpoint. The test was performed

according to the ISO 10712 method. An EC_{50} of ca. 213 mg/l was observed (Sepic, Bricelj, and Leskovsek, 2003).

The results of toxicity tests with microorganisms are listed in Table 2.

Table 12 Toxicity of phthalic anhydride and phthalic acid to microorganisms (IUCLID 4.4)

Test substance	Species	Endpoint	Parameter	Effects (nominal)	Reference
Phthalic anhydride	Activated sludge	ISO 8192	3 h-EC_{50}	> 1,000 mg/l (n)	Bayer AG, 1984
Phthalic acid	*Pseudomonas putida*	ISO 10712	16 h-EC_{50}	213 mg/l (n)	Sepic, Bricelj, and Leskovsek, 2003

4.2 Terrestrial Effects

No standard tests with phthalic anhydride on toxicity towards terrestrial animals and plants are available. However, the influence of phthalic acid on *Lactuca sativa* was tested.

The effect of phthalic acid on the inhibition of fruit germination of the plant *Lactuca sativa L. cv. Great Lakes* (common lettuce) was investigated. The fruits were sown on agar medium in plastic containers with lids at a temperature of 30 °C and germination was observed. A nominal IC_{50} of 731 mg/l was determined after 3 days (Reynolds, 1989).

Table 13 Toxicity of phthalic acid to terrestrial organisms (IUCLID 4.6.2)

Species	Endpoint	Effect concentration (nominal)	Reference
Lactuca sativa (terrestrial plant)	Inhibition of germination	3 d-IC_{50} = 731 mg/l	Reynolds, 1989

4.3 Other Environmental Effects

No data available.

4.4 Initial Assessment for the Environment

Phthalic anhydride forms white flakes or needles with a melting point of about 132 °C. The boiling point is 284.5 °C at 1013 hPa. The density is 1.527 g/cm^3 at 20 °C, the vapour pressure 0.0006 hPa at 26.6 °C, the log K_{OW} = 1.6. The flash point is about 152 °C, the auto flammability (ignition temperature) 580 °C. Phthalic anhydride hydrolyzes in water at pH 6.8 - 7.24 with half-lives of 0.5 - 1 min at 25 °C, forming phthalic acid, that has dissociation constants of about 2.8 and 5.4. Any phthalic anhydride emitted into the air or into the terrestrial compartment would be rapidly hydrolyzed by humidity in the air or in the soil, respectively.

In the atmosphere phthalic anhydride is degraded by photochemically produced OH radicals. The half-life is calculated to be about 21 days. For phthalic acid a half-life of 13 days is estimated. Removal of phthalic acid in sea water was proved to be influenced by light.

Phthalic anhydride is readily biodegradable. In an aquatic ready test system (aerobic) conducted according to OECD TG 301D, > 70 % biodegradation was reported after 30 days for phthalic anhydride as well as for its degradation product, phthalic acid.

Due to the rapid hydrolysis of phthalic anhydride in water, the distribution of the hydrolysis product phthalic acid is calculated. According to the Mackay fugacity model level I, the favourite target compartment of phthalic acid is water with 99.9 %.

The calculated Henry's law constants (2.21×10^{-7} Pa m^3/mol at 25 °C for phthalic acid, and 0.64 Pa m^3/mol at 25 C for phthalic anhydride) prove a low potential for volatilization from surface waters.

The bioconcentration factors (BCF) of 3.4 for phthalic anhydride and 3.16 for phthalic acid, calculated from the octanol-water partition coefficients, indicate that there is a low potential for bioaccumulation of phthalic anhydride and phthalic acid in aquatic organisms. Tests with ^{14}C-phthalic acid in plants indicate a low potential of phthalic anhydride and phthalic acid for bioaccumulation in plants.

Experimentally obtained adsorption coefficients (K_{OC}) revealed a low sorption potential of phthalic acid. The experimentally achieved K_{OC} values were in the range of 2 to 31 depending on soil properties. In addition, K_{oc} values were calculated with PCKOCWIN v. 1.66 (K_{OC} = 11 for phthalic anhydride, and K_{OC} = 73 for phthalic acid). These results indicate a low sorption potential of phthalic anhydride and phthalic acid onto the organic phase of soil or sediments.

Concerning the toxicity of phthalic anhydride and its hydrolysis product phthalic acid to aquatic species reliable experimental results of tests with fish, *Daphnia*, and algae are available. The result for algae refers both to growth rate and biomass. The tests were performed according to standard procedures or similar methods. The lowest effect values from the aquatic toxicity tests are (n = nominal concentration):

Cyprinus carpio	48 h-LC_{50}	> 500 mg/l (n) (phthalic acid)
Danio rerio	7 d-LC_{50}	= 560 mg/l (n)
Oncorhynchus mykiss (*S. gairdneri*)	60 d-NOEC	= 10 mg/l (n)
Daphnia magna	24 h-EC_{50}	= 140 mg/l (n) (phthalic acid)
Desmodesmus subspicatus	72 h-EC_{50}	≥ 100 mg/l (n) (phthalic acid)
Desmodesmus subspicatus	72 h-NOEC	≥ 100 mg/l (n) (phthalic acid).

Since chronic toxicity tests are available for fish and algae with phthalic anhydride and phthalic acid, respectively, an assessment factor of 50 can be applied using the lowest available effect concentration (NOEC = 10 mg/l) which was obtained for *Oncorhynchus mykiss* (*Salmo gairdneri*). Calculation yielded a

$PNEC_{aqua}$ of 200 µg/l.

5 RECOMMENDATIONS

Human Health:

The chemical is a candidate for further work.

The chemical possesses properties indicating a hazard for human health (irritation of skin and respiratory system, serious eye damage, respiratory and skin sensitization). Based on data presented by the Sponsor country, adequate risk management measures are being applied for occupational settings. A potential for consumer exposure exists as a result of its use in plastics, furniture and home products. It is therefore recommended to perform an exposure assessment and, if then indicated, a risk assessment.

Environment:

The chemical is currently of low priority for further work because of its low hazard profile.

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I U C L I D

Data Set

Existing Chemical	:	ID: 85-44-9
CAS No.	:	85-44-9
EINECS Name	:	phthalic anhydride
EC No.	:	201-607-5
TSCA Name	:	1,3-Isobenzofurandione
Molecular Formula	:	C8H4O3

Producer related part

Company	:	Bayer AG
Creation date	:	27.07.1992

Substance related part

Company	:	Bayer AG
Creation date	:	27.07.1992
Status	:	
Memo	:	X Update 1998 AKTUELL EG / ICCA
Printing date	:	05.05.2006
Revision date	:	02.06.1994
Date of last update	:	04.05.2006
Number of pages	:	166
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

Type : lead organisation
Name : Bayer AG
Contact person :
Date :
Street :
Town : 51368 Leverkusen
Country : Germany
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

11.01.2005

Type : cooperating company
Name : Atofina
Contact person :
Date :
Street : 4-8, cours Michelet La Défense 10
Town : 95091 Paris La Défense Cedex
Country : France
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

12.11.2004

Type : cooperating company
Name : BASF AG
Contact person :
Date :
Street : Karl-Bosch-Str
Town : 67056 Ludwigshafen
Country : Germany
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

12.11.2004

Type : cooperating company
Name : Exxon Chemical Europe Inc.
Contact person :
Date :
Street : 280 Boulevard du Souverain
Town : 1160 Bruxelles
Country : Belgium
Phone : (32) 2 674 44 16
Telefax : (32) 2 674 44 06

Telex : 22364
Cedex :
Email :
Homepage :

12.11.2004

Type : cooperating company
Name : LONZA AG
Contact person :
Date :
Street : Muenchensteinerstrasse 38
Town : 4002 Basel
Country : Switzerland
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

12.11.2004

Type : cooperating company
Name : Perstorp SpA,Div. Polyols
Contact person :
Date :
Street : Via Sempione 13
Town : I-21053 Castellanza(VA)
Country : Italy
Phone : 0331-523405
Telefax : 0331-670190
Telex : 323652
Cedex :
Email :
Homepage :

12.11.2004

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

IUPAC Name : Phthalic anhydride
Smiles Code : O=C(OC(=O)c1cccc2)c12
Molecular formula : C8H4O3
Molecular weight : 148.12
Petrol class :

Flag : Critical study for SIDS endpoint

02.08.2004 (1)

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type : other: technical grade
Substance type : organic
Physical status : solid
Purity : >= 99.8 % w/w
Colour : White flakes or needles
Odour :

Result : · Maleic anhydride <= 0.05 % (specification limits, determined by GC) (Lorz, Towae, and Bhargava, 2002)
· Benzoic acid <= 0.1 % (specification limits, determined by GC) (Lorz, Towae and Bhargava 2002)
· Phthalic acid <= 0.1 % (specification limits) (BASF, 2000)
Flag : Critical study for SIDS endpoint
06.10.2005 (2) (3)

Purity type :
Substance type :
Physical status :
Purity :
Colour : white needles
Odour : aromatic

06.10.2005 (4)

1.1.2 SPECTRA

Type of spectra : UV

Method : The spectrum of a solution of phthalic anhydride in n-heptane, ethanol or diethyl ether was recorded on a Cary 219 spectrophotometer; no further details reported.
Result : Extinction coefficients at absorption maxima:

Wave length (nm)	log E
294	3.28
285	3.18
279 (shoulder)	2.99
245	3.56
213	4.40
210	4.46

11.01.2005 (5)

1.2 SYNONYMS AND TRADENAMES

Phthalic acid anhydride

Flag : Critical study for SIDS endpoint
30.09.2004 (6)

1,3-Isobenzofurandione

Flag : Critical study for SIDS endpoint

30.09.2004 (6)

Isobenzofuran-1,3-dione

Flag : Critical study for SIDS endpoint
30.09.2004

1,2-Benzenedicarboxylic acid anhydride

Flag : Critical study for SIDS endpoint
30.09.2004 (6)

1,2-Benzenedicarboxylic anhydride

Flag : Critical study for SIDS endpoint
30.09.2004 (6)

1,3-Dihydro-1,3-dioxoisobenzofurane

Flag : Critical study for SIDS endpoint
30.09.2004

1,3-Dioxophthalane

Flag : Critical study for SIDS endpoint
30.09.2004 (6)

1,3-Phthalandione

Flag : Critical study for SIDS endpoint
30.09.2004 (6)

Phthalandione

Flag : Critical study for SIDS endpoint
30.09.2004

Isobenzofurane, 1,3-dihydro-1,3-dioxo-

Flag : Critical study for SIDS endpoint
30.09.2004

1,3 Phthalandione

27.09.2004 (6)

Phthalic anhydride

Flag : Critical study for SIDS endpoint
28.09.2004 (7)

1.3 IMPURITIES

Purity : other: technical grade
CAS-No : 108-31-6
EC-No : 203-571-6
EINECS-Name : maleic anhydride
Molecular formula : C4H2O3
Value : <= .05 % w/w

Result : Specification limits, determined by GC
Flag : Critical study for SIDS endpoint
23.11.2004 (3)

Purity : other: technical grade
CAS-No : 65-85-0
EC-No : 200-618-2
EINECS-Name : benzoic acid
Molecular formula : C7H6O2
Value : <= .1 % w/w

Result : Specification limits, determined by GC
Flag : Critical study for SIDS endpoint
30.09.2004 (3)

Purity : other: technical grade
CAS-No : 88-99-3
EC-No : 201-873-2
EINECS-Name : phthalic acid
Molecular formula : C8H6O4
Value : <= .1 % w/w

Flag : Critical study for SIDS endpoint
06.10.2005 (2)

Purity : other: · Technical product in the early 1950ies
CAS-No :
EC-No :
EINECS-Name : Naphthoquinone
Molecular formula : C10H6O2
Value :

Remark : Historic data. The study is of 1955 and describes a product which is not identical with the product of the Sponsor company
06.10.2005 (8)

1.4 ADDITIVES

1.5 TOTAL QUANTITY

Quantity : 3232000 - tonnes produced in 2000

Remark : Estimated world wide production volume with the following regional distribution:

Region	Estimated production volume (tonnes/a)
Western Europe	770,000
Eastern Europe	171,000
Japan	302,000
Middle East	75,000
Other Asia	1,156,000
USA	485,000
Mexico/South + Central America	249,000
Others	24,000

Flag : Critical study for SIDS endpoint
23.11.2004 (9)

1.6.1 LABELLING

Labelling : as in Directive 67/548/EEC
Specific limits :
Symbols : Xn, , ,
Nota : , ,
R-Phrases : (22) Harmful if swallowed
(37/38) Irritating to respiratory system and skin
(41) Risk of serious damage to eyes
(42/43) May cause sensitization by inhalation and skin contact
S-Phrases : (23) Do not breathe vapour/spray
(24/25) Avoid contact with skin and eyes
(26) In case of contact with eyes, rinse immediately with plenty of water and seek medical advice
(37/39) Wear suitable gloves and eye/face protection
(46) If swallowed, seek medical advice immediately and show this container or label

28.09.2004 (10)

1.6.2 CLASSIFICATION

Classified : as in Directive 67/548/EEC
Class of danger : harmful
R-Phrases : (22) Harmful if swallowed
Specific limits :

28.09.2004 (10)

Classified : as in Directive 67/548/EEC
Class of danger : irritating
R-Phrases : (37/38) Irritating to respiratory system and skin
(41) Risk of serious damage to eyes
Specific limits :

28.09.2004 (10)

Classified : as in Directive 67/548/EEC
Class of danger : sensitizing
R-Phrases : (42/43) May cause sensitization by inhalation and skin contact
Specific limits :

28.09.2004 (10)

1.6.3 PACKAGING

1.7 USE PATTERN

Type of use : type
Category : Non dispersive use

Flag : Critical study for SIDS endpoint
30.09.2004 (11)

Type of use : industrial
Category : Chemical industry: used in synthesis

Flag : Critical study for SIDS endpoint
30.09.2004 (11)

Type of use : use
Category : Intermediates

Flag : Critical study for SIDS endpoint
30.09.2004 (11)

Type of use : use
Category : Intermediates

Remark : EPA (1994a) reports that phthalic anhydride is also used for tanning and curing of leather products. In another publication of the same year, EPA (1994b) reports that "Companies use phthalic anhydride to make halogenated anhydrides used as fire retardants; polyester polyols for urethanes; phthalocyanine pigments; dyes; perfumes; pharmaceuticals; tanning and curing agents; solvents; insect repellents; and various chemical intermediates."
For chrome tannage, phthalic acid/sodium phthalate is an important auxiliary (EU, 2003) and can easily be made from phthalic acid. Thus, it is likely that EPA (1994a) meant that phthalic anhydride is used to make tanning and curing agents. However, since leather is tanned in aqueous solution, phthalic anhydride cannot persist to occur in tanned consumer products.
30.09.2004 (12) (13) (14)

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

Type of limit : MAK (DE)
Limit value :

Remark : Paragraph IIb. Substances for which no MAK-value can be derived at the moment (MAK: maximun admissible concentration)
Flag : Critical study for SIDS endpoint
29.09.2004 (15)

Type of limit : TLV (US)
Limit value : 1 other: ppm

28.09.2004 (16)

Type of limit : other: TRGS 900
Limit value : 1 mg/m3

Remark : 1 mg/m3 (inhalable fraction)

This concentration should never be exceeded
29.09.2004 (17)

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

Classified by : KBwS (DE)
Labelled by : KBwS (DE)
Class of danger : 1 (weakly water polluting)

Remark : Offical German Classification with identification number (Kenn-Nr.) 732
25.11.2004 (18)

1.8.4 MAJOR ACCIDENT HAZARDS

Legislation : Stoerfallverordnung (DE)
Substance listed : no
No. in Seveso directive :

28.09.2004 (19)

1.8.5 AIR POLLUTION

Classified by : TA-Luft (DE)
Labelled by : TA-Luft (DE)
Number : other: 5.2.5 organic substances
Class of danger : I

Remark : The particulate matter in the exhaust shall not exceed the limit value of 0.10 kg/h or the concentration of 20 mg/m3
29.09.2004 (20)

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

Type : degradation product in water
CAS-No : 88-99-3
EC-No : 201-873-2
EINECS-Name : phthalic acid
IUCLID Chapter : 3.1.2 and 3.5

Flag : Critical study for SIDS endpoint
02.08.2004 (21)

Type : degradation product in water
CAS-No : 124-38-9
EC-No : 204-696-9
EINECS-Name : carbon dioxide
IUCLID Chapter : 3.5

Remark : Experiment carried out in a model ecosystem containing algae, invertebrates and vertebrates
Flag : Critical study for SIDS endpoint
23.11.2004 (22)

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

1.11 ADDITIONAL REMARKS

Memo : NIOSH National Occupational Exposure Survey (1981 - 1983)

Result : In 1981-1983 approximately 81000 workers were potentially exposed to phthalic anhydride in the USA
Flag : Critical study for SIDS endpoint
31.10.2005 (23)

1.12 LAST LITERATURE SEARCH

Type of search : Internal and External
Chapters covered : 1
Date of search : 03.02.2004

28.09.2004

Type of search : Internal and External
Chapters covered : 2
Date of search : 03.02.2004

28.09.2004

Type of search : Internal and External
Chapters covered : 3, 4
Date of search : 03.02.2004

28.09.2004

Type of search : Internal and External
Chapters covered : 5
Date of search : 22.01.2004

29.09.2004

1.13 REVIEWS

2.1 MELTING POINT

Value : 131.6 °C
Sublimation :
Method :
Year : 1991
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Remark : Same data reported in Lide DR (1991). Handbook of Chemistry and Physics. CRC Press, Boston, 72nd Edition, 3-401.
Reliability : (2) valid with restrictions
Data from peer-reviewed handbook or collection of data
Flag : Critical study for SIDS endpoint
24.06.2004 (3)

Value : 131 - 132 °C
Sublimation :
Method :
Year : 1992
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Reliability : (2) valid with restrictions
Data from peer-reviewed handbook or collection of data
18.06.2004 (24)

Value : 123 - 134 °C
Sublimation :
Method :
Year : 2003
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Result : Beilstein reports several melting point values from 36 original references. Reported values were between 123 and 134°C, values in the range of 131-132°C were abundant.
Reliability : (2) valid with restrictions
Data from peer-reviewed handbook or collection of data
23.11.2004 (25)

Value : 130.8 °C
Sublimation :
Method :
Year : 2001
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Reliability : (2) valid with restrictions
Data from peer-reviewed handbook or collection of data
21.07.2004 (26)

Value : 131 °C
Sublimation :
Method :
Year : 2003
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Reliability : (2) valid with restrictions
Data from peer-reviewed handbook or collection of data
13.07.2004 (27) (4)

Value : 130.8 °C
Sublimation :
Method :
Year : 1996
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Reliability : (4) not assignable
Data from non peer-reviewed handbook or collection of data
18.06.2004 (28)

Value : 131.2 °C
Sublimation :
Method :
Year : 1979
GLP : no
Test substance : other TS: phthalic anhydride, purity is not specified

Reliability : (4) not assignable
Data from non peer-reviewed handbook or collection of data
06.10.2005 (29)

Value : 131 °C
Sublimation :
Method :
Year : 2002
GLP : no data
Test substance : other TS: Phthalic anhydride, purity is not specified

Reliability : (4) not assignable
Manufacturer data without proof
29.07.2004 (30)

Value : 131.2 °C
Sublimation :
Method :
Year : 1993
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Reliability : (4) not assignable
Data from non peer-reviewed handbook or collection of data
24.06.2004 (31)

Value : 131.6 °C
Sublimation :
Method :
Year : 1988
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Reliability : (4) not assignable
Data from non peer-reviewed handbook or collection of data
18.06.2004 (32)

2.2 BOILING POINT

Value : 284.5 °C at
Decomposition :
Method :
Year :
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Reliability : (2) valid with restrictions
Data from peer-reviewed handbook or collection of data
Flag : Critical study for SIDS endpoint
23.11.2004 (24)

Value : 295 °C at 1013 hPa
Decomposition :
Method :
Year : 2000
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Reliability : (2) valid with restrictions
Data from peer-reviewed handbook or collection of data
23.11.2004 (3) (26)

Value : 295 °C at 1013 hPa
Decomposition :
Method :
Year : 1991
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Remark : Sublimation point
Reliability : (2) valid with restrictions
Data from peer-reviewed handbook or collection of data
06.10.2005 (33)

Value : 285 °C at
Decomposition :
Method :
Year : 2003
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Reliability : (2) valid with restrictions
Data from peer-reviewed handbook or collection of data
18.06.2004 (4)

Value : 284 °C at 1013 hPa
Decomposition :
Method :
Year : 2004
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Result : No boiling point assigned: sublimes
Reliability : (2) valid with restrictions
Data from handbook or collection of data
29.07.2004 (27)

Decomposition :
Method :
Year : 2002
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Result : Beilstein reports several boiling point values from 7 original references:

Temperature, °C	at pressure, Torr	(hPa)
276		
284.5	760	(1013)
282.5	729	(970)
281.8	719	(956)
193.6	80	(106)
150	12	(16)
126 - 127	2	(2.7)

Reliability : (2) valid with restrictions
Data from peer-reviewed handbook or collection of data
29.07.2004 (25)

Value : 295 °C at 1013 hPa
Decomposition :
Method :
Year : 1979
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Reliability : (4) not assignable
Data from non peer-reviewed handbook or collection of data
06.10.2005 (29)

Value : 284.5 °C at 1013 hPa
Decomposition :
Method :
Year : 1968
GLP : no
Test substance : other TS: phthalic anhydride, purity is not specified

Result : No boiling point assigned: sublimation
Reliability : (4) not assignable
Data from non peer-reviewed handbook or collection of data
22.07.2004 (32) (34) (28)

Value : 285 °C at 1013 hPa
Decomposition :
Method :
Year : 1993
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Remark : Sublimes below boiling point
Reliability : (4) not assignable
Data from non peer-reviewed handbook or collection of data
22.07.2004 (31)

2.3 DENSITY

Type : density

Value : 1.527 g/cm³ at 20 °C
Method :
Year : 2002
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Result : Beilstein reports several values of density of the liquid (crystal) from 5 (2) original references:

value	ref. temp., °C	meas. temp., °C
1.527	4	
1.527		20
1.238		130
1.20116	4	150
1.17095	4	180

Reliability : (2) valid with restrictions
Data from peer-reviewed handbook or collection of data
Flag : Critical study for SIDS endpoint
29.07.2004 (25)

Type : density
Value : 1.527 g/cm³ at 4 °C
Method :
Year : 2002
GLP : no
Test substance : other TS: phthalic anhydride, purity is not specified

Reliability : (2) valid with restrictions
Data from peer-reviewed handbook or collection of data
06.10.2005 (3)

Type : relative density
Value : 1.53 g/cm³ at 20 °C
Method :
Year : 2004
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Reliability : (2) valid with restrictions
Data from handbook or collection of data
23.11.2004 (27)

Type : density
Value : 1.527 at °C
Method :
Year : 2003
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Reliability : (2) valid with restrictions
Data from peer-reviewed handbook or collection of data
06.10.2005 (4)

Type : density
Value : 1.53 at °C
Method :
Year : 2001
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Reliability : (2) valid with restrictions

Data from peer-reviewed handbook or collection of data
23.06.2004 (26)

Type : density
Value : 1.53 at 4 °C
Method :
Year : 1996
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Reliability : (4) not assignable
Data from non peer-reviewed handbook or collection of data
21.07.2004 (28)

Type : density
Value : 1.527 g/cm³ at 4 °C
Method :
Year : 1968
GLP : no
Test substance : other TS: solid (4°C) and molten phthalic anhydride, purity is not specified

Result : temperature, °C density, g/ml
135 1.208
140 1.202
160 1.181
180 1.161
200 1.142
220 1.124
240 1.105
Reliability : (4) not assignable
Data from non peer-reviewed handbook or collection of data
23.11.2004 (34)

Type : density
Value : 1.527 g/cm³ at 4 °C
Method :
Year : 1979
GLP : no
Test substance : other TS: phthalic anhydride, purity is not specified

Reliability : (4) not assignable
Data from non peer-reviewed handbook or collection of data
06.10.2005 (32) (31) (29)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : .0006 hPa at 26.6 °C
Decomposition :
Method : other (measured): see method
Year : 1946
GLP : no
Test substance : other TS: phthalic anhydride, purity not specified

Method : For temperatures between 30° and 60°C, Menzies's method was used, in which the vapour displaces permanent gas from a vessel of known volume

at the temperature at which the vapour pressure is to be measured into another volume, including a McLeod gauge, at a constant temperature. The vapour pressure is prevented from diffusing from one vessel to the other by a cold trap.
For temperatures between 90° and 145°C, the vapour pressure was measured directly on a mercury manometer completely immersed in a thermostat so that the vapour pressure of mercury and the effects of surface tension were identical in both limbs.

Result : Observed values are in the range of 0.000041 - 13.2 hPa at a temperature of 1.5-143.2 °C.
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
30.11.2004 (35)

Value : ca. 173.6 - 1009.9 hPa at °C
Decomposition :
Method :
Year : 2002
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Result : other values are:
ca. 1.33 - 1010.8 hPa at 96.5 - 284.5 °C
ca. 0.0004 - 13.1 hPa at 1.5 - 143.2 °C
Test condition : Temperature from 212 - 284.6 °C
Reliability : (2) valid with restrictions
Data from peer-reviewed handbook or collection of data
29.07.2004 (25)

Value : < .003 hPa at 20 °C
Decomposition :
Method :
Year : 2004
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Reliability : (2) valid with restrictions
Data from peer-reviewed handbook or collection of data
25.11.2004 (27)

Value : .000689 hPa at 25 °C
Decomposition :
Method : other (measured): Mcleod gage method
Year : 1960
GLP : no data
Test substance : other TS: phthalic anhydride

Remark : The equation log p = B - A/T, obtained from Crooks (1946), was used, where p is the pressure of saturated vapour in mmHg at the absolute temperature of T in Kelvin. The constants A (4632) and B (12.249) are valid for the temperature range of 30 to 60 °C. Thus, the value for 25 °C is extrapolated from 30 °C
Reliability : (2) valid with restrictions
Basic data given
29.07.2004 (36)

Value : .00027 hPa at 20 °C
Decomposition :
Method :

Year : 1988
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Result : other values: 0.0013 hPa at 30 °C and 0.02 hPa at 50 °C
Reliability : (4) not assignable
Data from non peer-reviewed handbook or collection of data
23.06.2004 (32)

Value : < .01 hPa at 20 °C
Decomposition :
Method :
Year : 2002
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Reliability : (4) not assignable
Manufacturer data without proof
22.07.2004 (30)

Value : ca. .00027 hPa at 20 °C
Decomposition :
Method :
Year : 1996
GLP : no
Test substance : other TS: phthalic anhydride

Result : another value: ca. 0.0013 hPa at 30 °C
Reliability : (4) not assignable
Data from non peer-reviewed handbook or collection of data
25.06.2004 (28)

Decomposition :
Method :
Year : 1968
GLP : no
Test substance : other TS: molten phthalic anhydride, purity is not specified

Result : temperature, °C vapour pressure, mmHg (hPa)

132	6	(8)
135	7	(9.33)
140	8.7	(11.6)
160	20.5	(27.3)
180	41	(54.7)
197	75	(100)
200	80.5	(107.3)
284.5	760	(1013)

Reliability : (4) not assignable
Data from non peer-reviewed handbook or collection of data
30.06.2004 (34)

Value : 1.33 hPa at 96.5 °C
Decomposition :
Method :
Year : 1979
GLP : no
Test substance : other TS: phthalic anhydride, purity is not specified

Reliability : (4) not assignable
Data from non peer-reviewed handbook or collection of data

06.10.2005 (29)

Value : ca. .032 hPa at 25 °C
Decomposition :
Method :
Year : 1994
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Remark : The equation used is valid only for the temperature range 404 - 791 K (= 131°C - 518°C). Thus, the above calculation is outside the range of the equation
Result : The value for 25 °C (298 K) is calculated with the following equation (in appendix C: Coefficients for vapor pressure equation):
log P = A + B/T + C log T + D T + E T² (P - mmHg, T - K),
where A = 30.6331
B = - 3.8783E+03
C = - 7.8671
D = 1.1148E-09
E = 2.5885E-06

Furthermore a curve is given of the pressure (psia) results in relation to the temperature (F). From this curve a pressure of 2 psia (ca. 140 hPa) at a temperature of 400 F (204.4 °C) can be read. (1 psia = 6.895 kPa)
Reliability : (3) invalid
Significant methodological deficiencies

23.11.2004 (37)

2.5 PARTITION COEFFICIENT

Partition coefficient : octanol-water
Log pow : 1.6 at °C
pH value :
Method :
Year : 2004
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Reliability : (2) valid with restrictions
Data from peer-reviewed handbook or collection of data
Flag : Critical study for SIDS endpoint
23.07.2004 (27)

Partition coefficient :
Log pow : .73 at °C
pH value : 1
Method : other (calculated)
Year : 1995
GLP : no
Test substance : other TS: phthalic acid

Test substance : Phthalic acid is the major organic degradation product of phthalic anhydride hydrolysis
Reliability : (2) valid with restrictions
Data from peer-reviewed handbook or collection of data
Flag : Critical study for SIDS endpoint
25.11.2004 (38)

Partition coefficient : octanol-water

Log pow	:	2.07 at 25 °C
pH value	:	
Method	:	other (calculated): with SRC-KOWWIN v1.67, 2000
Year	:	2004
GLP	:	no
Test substance	:	other TS: phthalic anhydride, purity is not specified
Remark	:	The calculated value reflects the properties of the unhydrolyzed molecule without taking into account the sensitivity of phthalic anhydride towards hydrolysis
Reliability	:	(2) valid with restrictions Accepted calculation method

22.07.2004 (39)

Partition coefficient	:	octanol-water
Log pow	:	1.07 at 25 °C
pH value	:	
Method	:	other (calculated): with SRC-KOWWIN v1.67, 2000
Year	:	2004
GLP	:	no
Test substance	:	other TS: phthalic acid
Test substance	:	Phthalic acid is the major organic degradation product of phthalic anhydride hydrolysis
Reliability	:	(2) valid with restrictions Accepted calculation method

21.07.2004 (40)

Partition coefficient	:	octanol-water
Log pow	:	.7 at °C
pH value	:	
Method	:	
Year	:	1996
GLP	:	no data
Test substance	:	other TS: phthalic anhydride, purity is not specified
Result	:	0.73 (free acid at pH 1)
Reliability	:	(4) not assignable Data from non peer-reviewed handbook or collection of data

21.07.2004 (28)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in	:	Water
Value	:	16400 mg/l at 20 °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	
Deg. product	:	
Method	:	
Year	:	2000
GLP	:	no data
Test substance	:	other TS: phthalic anhydride, purity is not specified
Result	:	Solubility of phthalic anhydride in various solvents:

solvent	at °C	solubility
water	50	17400 mg/l
water	100	190000 mg/l
carbon disulfide	20	0.7 g/100g
formic acid	20	4.7 g/100g
pyridine	20	80 g/100g
benzene		soluble
ethanol	20	soluble
diethyl ether	20	slightly soluble

Reliability : (2) valid with restrictions
Data from peer-reviewed handbook or collection of data
Flag : Critical study for SIDS endpoint
23.07.2004 (3)

Solubility in : other: formic acid
Value : at 20 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :
Deg. product :
Method :
Year : 2003
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Result : 100 g solvent (formic acid) dissolves 4.7 g substance.
Furthermore values:
100 g solvent (pyridine) dissolves 80 g substance at 20-25°C.
100 part(s) of substance dissolves in 0.7 parts of solvent (CS2) at 20°C.
Reliability : (2) valid with restrictions
Data from peer-reviewed handbook or collection of data
21.07.2004 (25)

Solubility in : Water
Value : 6 g/l at 20 °C
pH value : 2
concentration : 6 g/l at 20 °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :
Deg. product :
Method :
Year : 2002
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Reliability : (4) not assignable
Manufacturer data without proof
25.11.2004 (30)

Solubility in : Water
Value : 6.4 g/l at 20 °C

pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :
Deg. product :
Method :
Year : 1996
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Remark : Phthalic anhydride hydrolyzes in water to phthalic acid
Reliability : (4) not assignable
Data from non peer-reviewed handbook or collection of data

21.07.2004 (28)

Solubility in : Water
Value : ca. 6.2 g/l at 25 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :
Deg. product :
Method :
Year : 1968
GLP : no
Test substance : other TS: phthalic anhydride, purity is not specified

Remark : Hydrolyzes in water
Result : Other approximate solubilities of phthalic anhydride:

solvent	temperature (°C)	measured value (g/100g)
water	135	95
carbon disulfide	20	0.7
formic acid (95%)	20	4.7
pyridine	20 - 25	80

Reliability : (4) not assignable
Data from non peer-reviewed handbook or collection of data

25.11.2004 (34)

Solubility in : other: alcohol, carbon disulfide, and hot water
Value : at °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :
Deg. product :
Method :
Year : 1993
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Result : soluble
Reliability : (4) not assignable
Data from non peer-reviewed handbook or collection of data
21.07.2004 (31)

2.6.2 SURFACE TENSION

Test type :
Value : 39.5 mN/m at 130 °C
Concentration :
Method :
Year : 2003
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Remark : Molten phthalic anhydride
Result : other values are:
32.7 mN/m at 180 °C
35.49 mN/m at 155 °C
Reliability : (2) valid with restrictions
Data from peer-reviewed handbook or collection of data
06.10.2005 (25)

Test type :
Value : 35.49 mN/m at 155 °C
Concentration :
Method :
Year : 1968
GLP : no
Test substance : other TS: phthalic anhydride, purity is not specified

Remark : Molten phthalic anhydride
Result : another value is: 32.70 mN/m at 180 °C
Reliability : (4) not assignable
Data from non peer-reviewed handbook or collection of data
06.10.2005 (34)

2.7 FLASH POINT

Value : 152 °C
Type : closed cup
Method :
Year : 2004
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Reliability : (2) valid with restrictions
Data from peer-reviewed handbook or collection of data
Flag : Critical study for SIDS endpoint
25.11.2004 (27)

Value : 151.7 °C
Type : closed cup
Method :
Year : 1979
GLP : no

Test substance : other TS: phthalic anhydride, purity is not specified

Reliability : (4) not assignable
Data from non peer-reviewed handbook or collection of data
06.10.2005 (29)

Value : 152 °C
Type : closed cup
Method :
Year : 2002
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Reliability : (4) not assignable
Manufacturer data without proof
30.06.2004 (30)

Value : 151.6 °C
Type : closed cup
Method :
Year : 1993
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Reliability : (4) not assignable
Data from non peer-reviewed handbook or collection of data
30.06.2004 (31)

Value : 151 °C
Type : closed cup
Method :
Year : 1968
GLP : no
Test substance : other TS: phthalic anhydride as a molten liquid, purity is not specified

Result : The flash point of type 'open cup' is at 165 °C.
Reliability : (4) not assignable
Data from non peer-reviewed handbook or collection of data
30.06.2004 (34)

2.8 AUTO FLAMMABILITY

Value : 580 °C at
Method :
Year : 2000
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Reliability : (2) valid with restrictions
Data from peer-reviewed handbook or collection of data
Flag : Critical study for SIDS endpoint
22.07.2004 (3)

Value : 570 °C at
Method :
Year : 1979
GLP : no
Test substance : other TS: phthalic anhydride, purity is not specified

Reliability : (2) valid with restrictions
Data from peer-reviewed handbook or collection of data
22.07.2004 (27)

Value : 570 °C at
Method :
Year : 1979
GLP : no
Test substance : other TS: phthalic anhydride, purity is not specified

Reliability : (4) not assignable
06.10.2005 (29)

Value : 583 °C at
Method :
Year : 1993
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Reliability : (4) not assignable
Data from non peer-reviewed handbook or collection of data
24.06.2004 (31)

Value : 584 °C at
Method :
Year : 1968
GLP : no
Test substance : other TS: phthalic anhydride as a molten liquid, purity is not specified

Reliability : (4) not assignable
Data from non peer-reviewed handbook or collection of data
30.06.2004 (34)

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

Method :
Year : 2004
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Reliability : (2) valid with restrictions
Data from peer-reviewed handbook or collection of data
19.07.2004 (27)

Result : other: Explosive limits in air: 1.7 - 10.5 % v/v
Method :
Year : 2002
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Reliability : (2) valid with restrictions
Data from peer-reviewed handbook or collection of data
06.10.2005 (3)

Result : other: Explosive limits in air: 1.7 - 10.4 % v/v

Method :
Year : 1979
GLP : no
Test substance : other TS: phthalic anhydride, purity is not specified

Reliability : (4) not assignable
Data from peer-reviewed handbook or collection of data
06.10.2005 (29)

Result : other: Explosive limits in air: 1.7 - 10.5 % v/v
Method :
Year : 2002
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Reliability : (4) not assignable
Manufacturer data without proof
06.10.2005 (30)

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

Acid-base constant : Second Dissociation Constant pka2
Method : other
Year : 1945
GLP : no
Test substance : other TS: o-Phthalic acid (CAS-Nr. 88-99-3)

Method : Measurements of potential difference between hydrogen electrodes and silver-silver-chloride electrodes in aqueous solutions of 72 different phthalate-chloride mixtures at 13 temperatures from 0 ° to 60 °C were made.

The second dissociation constant of o-phthalic acid was evaluated from the experimental data.

Result : Average value of pka2 at different temperature:

5.43 +/- 0.0007 (0 °C)
5.41 +/- 0.0008 (25 °C)
5.54 +/- 0.0009 (60 °C)

Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
09.07.2004 (41)

Method : other
Year : 1979
GLP : no
Test substance : other TS: phthalic acid, purity not specified

Result : Dissociation constants (pka1, pka2), measured at different temperatures:

	pka1	pka2
25 °C	2.76	4.92
	2.63	4.73
	3.05	4.89
35 °C	2.97	5.43

Reliability : (2) valid with restrictions
Data from peer-reviewed handbook or collection of data
Flag : Critical study for SIDS endpoint
29.07.2004 (42)

Method :
Year : 1975
GLP : no
Test substance : other TS: phthalic acid, purity is not specified

Result : pKa = 2.95 and 5.41 at 25 °C.
The pKa data were reported in the score of a study on the inhibition of fruit germination of lettuce (cf. Chapter 4.6.2).
Reliability : (4) not assignable
Documentation insufficient for assessment
19.07.2004 (43)

2.13 VISCOSITY

Test type : other: Dynamic viscosity
Test procedure :
Value : = 1.125 - mPa s (dynamic) at 155 °C
Result :
Method :
Year : 2003
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Result : another value is: 0.875 mPa s at 180 °C.
Reliability : (2) valid with restrictions
Data from peer-reviewed handbook or collection of data
23.06.2004 (25)

Method :
Year : 1968
GLP : no
Test substance : other TS: molten phthalic anhydride, purity is not specified

Result : temperature, °C viscosity, mP
132 11.9
197 6.4
220 5.5
Reliability : (4) not assignable
Data from non peer-reviewed handbook or collection of data
30.06.2004 (34)

2.14 ADDITIONAL REMARKS

Memo : pH of solution

Result : observed pH of 2.80 at 731 +/- 100 mg/l (4.4 +/- 0.6 mM)
Reliability : (4) not assignable
Documentation insufficient for assessment
06.10.2005 (43)

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
Conc. of substance	:	at 25 °C
INDIRECT PHOTOLYSIS		
Sensitizer	:	OH
Conc. of sensitizer	:	500000 molecule/cm³
Rate constant	:	.00000000000007492 cm³/(molecule*sec)
Degradation	:	50 % after 21.4 day(s)
Deg. product	:	
Method	:	other (calculated): with SRC-AOPWin v1.91, 2000
Year	:	2004
GLP	:	no
Test substance	:	other TS: phthalic anhydride
Remark	:	The calculated half-life is based on a mean OH concentration of 0.5E+6 OH radicals/cm³ as 24 h average The calculated value reflects the properties of the unhydrolyzed molecule without taking into account the sensitivity of phthalic anhydride towards hydrolysis
Reliability	:	(2) valid with restrictions Accepted calculation method
Flag	:	Critical study for SIDS endpoint

06.10.2005 (39)

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
INDIRECT PHOTOLYSIS		
Sensitizer	:	OH
Conc. of sensitizer	:	500000 molecule/cm³
Rate constant	:	.0000000000001237 cm³/(molecule*sec)
Degradation	:	50 % after 13 day(s)
Deg. product	:	
Method	:	other (calculated): with SRC-AOPWin v1.91, 2000
Year	:	2004
GLP	:	no
Test substance	:	other TS: phthalic acid
Remark	:	The calculated half-life is based on a mean OH concentration of 0.5E+6 OH radicals/cm³ as 24 h average
Test substance	:	Phthalic acid is the major organic degradation product of phthalic anhydride hydrolysis
Reliability	:	(2) valid with restrictions Accepted calculation method
Flag	:	Critical study for SIDS endpoint

06.10.2005 (40)

Type	:	other: sea water
Light source	:	other: 380 W mercury arc
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
Deg. product	:	
Method	:	other (measured):

Year	:	1968
GLP	:	no
Test substance	:	other TS: phthalic acid, purity is not specified
Method	:	A photochemical air-cooled reactor, using a medium-power mercury arc lamp for oxidation of organic matter in seawater.
Result	:	First order rate constant (hours E-1) for photooxidation in sea water was 0.75. That is equivalent with a half-life of 0.93 hours.
Test condition	:	- medium: sea water, irridiation for 24 hours, saturated with oxygen at 50 °C - test concentration: 1 mmol/l - test procedure: in an air-cooled reactor in which twelve samples in silica tubes could be irradiated known concentration of the test substance was placed - pretreatment of sea-water: sea water was added with avoidance of entrapped air bubbles; overnight irradiation time between 15 - 16 hours; temperature 50 °C
Reliability	:	(2) valid with restrictions The study is well documented and meets generally accepted scientific principles for assessment
Flag	:	Critical study for SIDS endpoint

29.11.2004 (44)

Type	:	water
Light source	:	other: mercury lamp and sunlight
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
DIRECT PHOTOLYSIS		
Halflife t1/2	:	3.9 - 9.6 hour(s)
Degradation	:	% after
Quantum yield	:	
Deg. product	:	yes
Method	:	other (measured)
Year	:	1991
GLP	:	no data
Test substance	:	other TS: Phthalic anhydride, purity 99.8 %
Deg. products	:	polyphenyl
Result	:	Phthalic anhydride hydrolyzed to phthalic acid. Small quantities of benzoic acid were found. Polyphenyl (1,4´-bonds dominating) with a molecular weight of predominantly 2800 - 3600 g/mol was formed by decarboxylation of phthalic acid under anaerobic conditions. The half lives of phthalic anhydride were 3.9 h (distilled water), 6.3 h (riverine water), 6.8 h (artificial sea water), and 9.6 h (natural sea water) under anaerobic conditions. It was assumed that the retardation of photodegradation of phthalic acid in sea water and river water was due to halides and humic compounds
Test condition	:	Distilled water, riverine water, natural sea water and artificial sea water were filtered through membrane filters (0.22 µm pore size) and spiked with phthalic anhydride (0.002 mol/l). While being purged with nitrogen the solutions were irradiated with sunlight (15 days) or with a medium pressure mercury lamp (12 hours) that emits mainly in the region 365-366 nm and to a lesser extend at 265, 297, 303, 313 and 334 nm. The products were extracted from the mixture that was evaporated to dryness before. The products were analysed by GC-FID. Polyphenyl formed during the irradiation was analysed by gel permeation chromatography
Reliability	:	(2) valid with restrictions Basic data given

06.10.2005 (45)

3.1.2 STABILITY IN WATER

Type	:	abiotic
t1/2 pH4	:	at °C
t1/2 pH7	:	at °C
t1/2 pH9	:	at °C
Deg. product	:	yes
Method	:	other: measured
Year	:	2001
GLP	:	no data
Test substance	:	other TS: phthalic anhydride, purity is not specified
Deg. products	:	88-99-3 201-873-2 phthalic acid
Method	:	The rate of hydrolysis was determined at different pHs in the range of 0.63-10.50 at 25 °c and in water containing a small amount of acetonitrile. To regulate the pH in the different pH-ranges HCl and several buffers were used.
Result	:	Half-life* at 25 degree C at different pH-values in different buffer-systems: 1/2 (pH-values of 0-6) : 70 sec 1/2 (pH-value of 6.8, N-methyl imidazole): 61 sec 1/2 (pH-value of 7.24, phosphate) : 30.5 sec 1/2 (pH-value of 8.9, CO3/HCO3-) : 2.4 sec * calculated from the cited observed rate constants
Reliability	:	(2) valid with restrictions The study is well documented and meets generally accepted scientific principles for assessment
Flag	:	Critical study for SIDS endpoint

29.11.2004 (21)

Deg. product	:	
Method	:	
Year	:	2004
GLP	:	no data
Test substance	:	other TS: Phthalic acid
Remark	:	Phthalic acid is the final product of hydrolysis of phthalic anhydride
Result	:	Carboxylic acids are generally resistant to hydrolysis
Reliability	:	(2) valid with restrictions Data from peer-reviewed handbook or collection of data

06.10.2005 (46)

Type	:	abiotic
t1/2 pH4	:	at °C
t1/2 pH7	:	at °C
t1/2 pH9	:	at °C
Deg. product	:	
Method	:	other: measured
Year	:	1975
GLP	:	no
Test substance	:	other TS: Phthalic anhydride (B.D.H. reagent grade)
Method	:	The hydrolysis was followed by adding 1 drop of a stock solution in 1,4-dioxan to a 10 mm stoppered spectroscopy cell containing the reaction medium at the required temperature (25 °C) and following the decrease in optical density at 300 and 322 nm, respectively, with a Beckman DU Spectrometer.
Result	:	An estimated half-life of approximately 1.5 minutes was calculated using a

reported observed rate constant of 7.9X10-3/sec for hydrolysis. Hydrolysis in aqueous solution over range between 4 mol/l-HCl and sodium acetate-hydrochloric acid buffers from pH 0.63 - 5.2 at 25 °C resulted in an average reaction rate constant of 0.0216/sec

Reliability : (4) not assignable
Documentation insufficient for assessment

29.11.2004 (47)

Type : abiotic
t1/2 pH4 : at °C
t1/2 pH7 : at °C
t1/2 pH9 : at °C
Deg. product :
Method : other
Year : 1963
GLP : no
Test substance : other TS: Phthalic anhydride, purity is not specified

Method : There is no information about the test procedure.
Result : First-order rate constant at 25.1 °C is 4.29E-04/sec
Test condition : Hydrolysis measured in dioxan-water (60:40 v/v) at 25 °C
Reliability : (3) invalid
Documentation insufficient for assessment

29.11.2004 (48) (49)

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

Type of measurement : background concentration
Media : drinking water
Concentration :
Method : GC/MS

Remark : US EPA (1994) noted that the presence of the phthalic anhydride in water could have resulted from the hydrolysis of phthalate esters followed by dehydration in the GC injection port. Thus, the significance of studies using similar GC techniques is rather limited because phthalic anhydride might be formed during these analytical procedures
Result : Phthalic anhydride has been identified, but not quantified, in US drinking water. US EPA states that this observation is presumably an artefact (see Remark). US EPA concluded that the rapid hydrolysis of phthalic anhydride to phthalic acid that occurs in aqueous media, would preclude any significant transport of the chemical in the aquatic environment
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
29.04.2004 (12)

Type of measurement : other: degradation of plasticizer (DEHP)
Media : other: plastic and plasticizer
Concentration :
Method : GC

Method : - To sample air was drawn through Tenax tubes (SKC-226-39)
- Desorption with methyl-t-butylether
- GC on fused silica column OV-225 at 60-200 °C, injector at 220 °C,

electron capture detector (63Ni)

Result : Both PVC (polyvinylchloride) containing DEHP (di-2-ethylhexylphthalate) as well as pure DEHP released phthalic anhydride which was formed during DEHP degradation at high temperatures.

Reliability : (2) valid with restrictions
Basic data given

Flag : Critical study for SIDS endpoint

14.05.2004 (50)

Type of measurement : background concentration
Media : food
Concentration :
Method : GC/MS

Method : - Approximately 250 kg Idaho potatoes (variety Russet Burbank) baked in aluminium foil at 205 °C for 105 min
- Volatile compounds isolated from head space
- GC over OV-101 (15 fractions), column temperature 40-250°C, no injector block temperature reported
- All fractions GC over SP-1000 (15 fractions)
- Each fraction GC/MS over OV-17
- Selected subfractions rechromatographed over OV-17 and GC/MS over SE-30
- In total 420 fractions obtained
- Identification of phthalic anhydride by MS and IR spectra
- Estimate for quantity by peak area comparison

Remark : Unfortunately the formation of phthalic anhydride is not discussed by the authors of the study.
Phthalic anhydride is put into the group of esters and lactones and it is stated that the esters were formed by esterification of various acids and alcohols present in potato flavor, and that the lactones were thermal decomposition products. For organic acids, it is stated that they are formed as thermal oxidative decomposition products of fats and by deamination of amino acids.

Result : Phthalic anhydride occurs in the volatile flavor of baked Idaho potatoes. In total 228 substances identified with ethyl acetate being the most abundant. The peak area of phthalic anhydride was 14 % of that of ethyl acetate.

Reliability : (2) valid with restrictions
Basic data given

Flag : Critical study for SIDS endpoint

29.11.2004 (51)

Type of measurement : concentration at contaminated site
Media : other: wastewater
Concentration :
Method : GC/MS

Method : - Fresh spruce chips dried
- Pulp prepared by cooking chips at 155 °C for 5 h, pH 4, with 6 % SO2, to reach kappa number 30 (= 4 % lignin)
- Part of pulp additionally treated with oxygen at 135 °C under elevated pressure for 95 min, diluted, washed and adjusted to pH 5 (kappa number 10)
- Chlorination of both pulps for 30 min at 20 °C, filtration and washing
- Filtration and washing media (1 l/100 g of pulp) combined and used as spent liquor
- Filtrations and adsorption on XAD-4 resin
- XAD-4 washed with methanol, diethylether, acetone, methanol, acetone
- XAD-4 eluted with large volume of diethylether

- GC (Finigan 9610)/MS (Finigan 4021) (injector at 250 °C), column temperature 30-300 °C
- Identification by comparison of mass spectra with NIH/EPA reference library
- Estimate for quantification by peak height comparison with dibutylphthalate which was quantified by GC

Remark : Phthalic anhydride might have been formed during analytical procedures e.g. from phthalic acid

Result : Phthalic anhydride was detected in spent chlorination liquor from bleaching of sulphite pulp (0.2-0.4 mg/kg). In total about 80 compounds were identified, mostly lignin degradation products

Reliability : (3) invalid
Significant methodological deficiencies

Flag : Critical study for SIDS endpoint
25.10.2005 (52)

Type of measurement : concentration at contaminated site
Media : sediment
Concentration :
Method : GC/MS

Method : - Sediment cores from Nervion river dumps (Nothern Spain) were obtained by fluid-free rotary drilling and freeze dried
- 30-40 g samples were extracted with methylenchloride/ methanol
- GC (Carlo Erba 5300 HRGC) was used with an injector temperature of 300 °C and a residence time of the sample of 35 s in the injector
- GC/MS: GC see above, transfer line from GC to MS 300 °C, ion source 200 °C, analyzer 230 °C

Remark : US EPA (1994) noted that the presence of the phthalic anhydride in water could have resulted from the hydrolysis of phthalate esters followed by dehydration in the GC injection port. Thus, the significance of studies using similar GC techniques is rather limited because phthalic anhydride might be formed during these analytical procedures

Result : Phthalic anhydride may be present in sediment cores of an uncontrolled hazardous waste dump in Northern Spain (Several polycyclic aromatic hydrocarbons are also found)

Reliability : (3) invalid
Significant methodological deficiencies

Flag : Critical study for SIDS endpoint
25.10.2005 (53)

Type of measurement : concentration at contaminated site
Media : sediment
Concentration :
Method : GC/MS

Method : - Sediment grab samples from two areas of the San Diego Harbor (CA, USA), stored at 4 °C
- Pyrolysis at up to 615 °C
- GC/MS
- Phthalic anhydride was not detected in samples not pyrolized (e.g. analysis by 13C NMR or thermochemolysis with tetramethylammonium hydroxide-GC/MS)

Remark : Since phthalic anhydride was only detected in pyrolized samples but not in samples analysed by GC/MS after a different preteatment, it is likely that phthalic anhydride was formed during the pyrolytic process

Result : Phthalic anhydride was detected in PAH contaminated sediments of San Diego Bay

Reliability : (3) invalid
Significant methodological deficiencies

Flag : Critical study for SIDS endpoint
25.10.2005 (54)

Type of measurement : concentration at contaminated site
Media : other: wastewater
Concentration :
Method : Biodegradation study, removal determined from COD and TOC

Remark : The wastewater treatment plant of the Kashima petroleum and petrochemical industrial complex (Japan) has a hydraulic retention time of approximately 14 h
Result : 88 % of the TOC of phthalic anhydride (influent concentration 65 mg/l) was removed from the authentic wastewater within 24 h during experimental incubations
Conclusion : Since the half-life of phthalic anhydride in aqueous solution is in the range of seconds to few minutes, it is assumed that not phthalic anhydride but phthalic acid persisted and that phthalic acid was the source of phthalic anhydride formed during analysis.
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
27.07.2004 (55) (56)

Type of measurement : other: wastewater treatment plant
Media : other: wastewater
Concentration :
Method : GC, GC/MS

Method : - Wastewater influent and effluent of the Prato (Italy) waterwater treatment plant sampled
- Filtration through glass fibre filter 0.45 µm
- Filtered wastewater saturated with sodium chloride and extracted with hexane; water phase adsorped on RP-18 column, eluted with acetone/hexane (1:10 v/v) and acetone; hexane-phase fractionated on silica gel column
- Particulate matter extracted with trichloromethane, followed by extraction with dichloromethane/methanol (2:1 v/v)
- Identification by GC, GC/MS (HPLC for PAH)
- GC: Varian 3400 with FID (flame ionization detector); injector temperature program 40-300 °C, 1 min at 300 °C; Supelco PTE-5 column 40-300 °C, 15 min at 300 °C
Result : The influent of the Prato municipal wastewater treatment plant contained phthalic anhydride, but not the effluent
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
24.05.2004 (57)

Type of measurement : background concentration
Media : ground water
Concentration :
Method : GC/MS

Method : - 20 l samples
- Sample clean up: Acidification, extraction with petrol ether and diethylether
- Extract concentrated to 1 ml, split
- Derivatisation with diazomethane
- GC (Pye 104 GC or Hewlett Packard 5710A GC): OV-1 (50-250°C [HP started at 80°C]) or FFAP (220 °C) resin columns, injector temperature 250

°C
- MS (First system: Pye 104 GC was combined with MS30): Injector temperature 250 °C, source temperature 200 °C
- MS (Second system: Hewlett Packard 5710A GC combined with VG 16F): Injector temperature 250 °C, source temperature 220 °C
- Substance identification by comparison with mass spectra library

Remark : Unfortunately, the distribution method of the ground water is not reported. Since several other compounds (e.g. benzyl cyanide, two C4 alkyl benzenes) stemmed from the distribution process, it appears that phthalic anhydride was formed during GC/MS analysis from phthalates or phthalic acid contaminating the groundwater during the distribution process.

Result : Phthalic anhydride was not found in freshly sampled groundwater. However, it was detected in the same groundwater after its distribution for drinking purposes. No phthalic anhydride could be detected in 12 other raw waters

Reliability : (2) valid with restrictions
Basic data given

Flag : Critical study for SIDS endpoint

29.04.2004 (58)

Type of measurement : background concentration
Media : drinking water
Concentration :
Method : no data

Result : Kool, van Kreijl, and Zoeteman (1982) cite a book of Zoeteman (1980) that phthalic anhydride occurs in drinking water. However, in the book of Zoetemann (1980), no information was found on the occurrence of phthalic anhydride in water

Reliability : (4) not assignable
Secondary literature

29.11.2004 (59) (60)

Type of measurement : concentration at contaminated site
Media : surface water
Concentration :
Method : Capillary GC/MS

Method : In the USA, 5 different methods were developed by the participating laboratories
- 3 methods used solid-phase extraction (SPE) of water followed by liquid chromatography (LC) and mass spectrometry with positive ion spray analysis (MS-ESI)
- 2 methods used continuous liquid-liquid extraction (CLLE) with capillary GC/MS
- Positive identification fulfilled the following criteria: -- Elution within the time frame set by standard reference compound
-- Sample spectrum and ion abundance to match that of the standard reference compound
- Quantification from base ion peak, two additional ions for confirmation

Result : In 15 out of 85 samples from contaminated water streams of the USA, phthalic anhydride was detected with an estimated maximum of 1 µg/l and a median of 0.7 µg/l in positive samples (limit of detection 0.25 µg/l). However, since the authors encountered phthalic anhydride routinely also in laboratory blanks, it is not clear whether phthalic anhydride is present in the tested US waters

Reliability : (4) not assignable
Documentation insufficient for assessment

Flag : Critical study for SIDS endpoint

05.10.2005 (61)

Type of measurement : background concentration
Media : surface water
Concentration :
Method : GC/MS

Method : - Sampling stations in the proximity of capture zones of drinking water plants
- Sampling in June 1991 and April 1992, using a Seastar A300 autosampler collecting 45 l of lakewater
- Samples filtered before extraction on column with Amberlite XAD-2 resin, column washed with methanol
- Elution of resin with acetone
- GC/MS Carlo Erba 5160 GC, equipped with MFA 515 injection programmer (injection on column with temperature programme from 100 to 250 °C, splitter closed for 60 sec) and ion trap detector Finnigan MAT 800. Fused-silica capillary column with SE-54 , column temperature 60-270 °C, transfer line temperature 200 °C

Remark : Unfortunately, the study was not printed correctly (Table 4), and its reliability cannot be elucidated
Result : Phthalic anhydride and several phthalates were detected in the three large Italian lakes (Como, Garda, and Maggiore) in 1991 and 1992.
Reliability : (4) not assignable
Documentation insufficient for assessment
Flag : Critical study for SIDS endpoint
18.05.2004 (62)

Type of measurement : concentration at contaminated site
Media : surface water
Concentration :
Method : GC/MS

Method : - From the Besos and Llobregat rivers (Barcelona, Spain), superficial water samples were collected from February to July 1986
- Sampling site for each river in the middle of the river bed, 5 km upstream estuary
- Samples concentrated 10 times, filtered, effluent directly assayed (titled dissolved water phase), filter cake extracted/resuspended in dimethylsulfoxide (titled paticulate water phase)
- Analysis by capillary GC (CGC) and negative ion chemical ionization (NICI) MS (Hewlett-Packard 5985A interphased with Hewlett-Packard 9825A data system); temperatures were at injector 300 °C, transfer line 290 °C, ion source 180 °C, and mass analyzer 120 °C
- Identification of substances by comparison of NICI mass spectra with standard library and by coinjection with authentic standard compounds (no information on purity of standard substance supplied)

Remark : GC/MS analysis was done under conditions which favor the formation of phthalic anhydride from phthalates or phthalic acid
Result : Phthalic anhydride was reported to be present in the dissolved fraction of water samples from the river Besos draining the heavily populated surroundings of Barcelona. These waters also contained several organic phthalates
Reliability : (3) invalid
Significant methodological deficiencies
07.10.2005 (63)

Type of measurement : background concentration
Media : surface water
Concentration :
Method : GC/MS

Remark	:	Original reference in Russian, only small summary available in English US EPA (1994) noted that the presence of the phthalic anhydride in water could have resulted from the hydrolysis of phthalate esters followed by dehydration in the GC injection port. Thus, the significance of studies using similar GC techniques is rather limited because phthalic anhydride might be formed during these analytical procedures
Result	:	In the River Dnepr and a freshwater reservoir, 0.2-5.2 µg/l phthalic anhydride were detected by GC/MS. Since these authors worked at high temperatures (up to 280 °C), it is assumed that phthalic anhydride was formed from phthalate (not specified which) present at 6.1-29.6 µg/l in the water samples.
Reliability	:	(3) invalid Significant methodological deficiencies
17.05.2004		(64)

Type of measurement	:	background concentration
Media	:	other: natural and drinking waters
Concentration	:	
Method	:	GC/MS
Remark	:	Since several phthalates were present in water samples, phthalic anhydride may have been formed from these compounds during GC/MS.
Result	:	Phthalic anhydride is reported to be present in samples of natural and/or drinking waters from the surroundings of Kiev
Reliability	:	(4) not assignable Original reference in Russian and not translated
07.10.2005		(65) (66)

Type of measurement	:	concentration at contaminated site
Media	:	surface water
Concentration	:	<= 10 mg/l
Method	:	no data
Remark	:	In Bajt, Sket and Faganelli (1992) it is reported, that the concentrations are unpublished results of M. Medved. No information supplied on method. It is not excluded that phthalic anhydride was formed as an artifact during GC.
Result	:	Wastewater of a chemical industry area at the Bay of Koper, Slovenia, was reported to contain phthalic anhydride at concentrations of up to 630 mg/l, and the water of the river Rizana, which enters the Bay of Koper, of up to 10 mg/l.
Reliability	:	(3) invalid Documentation insufficient for assessment
07.10.2005		(45)

Type of measurement	:	background concentration
Media	:	air
Concentration	:	
Method	:	no data
Result	:	Phthalic anhydride is an air polltant
Reliability	:	(4) not assignable Secondary literature
Flag	:	Critical study for SIDS endpoint
28.04.2004		(67)

Type of measurement	:	other: Photooxidation of naphthalene in the gas phase
Media	:	air
Concentration	:	
Method	:	GC-FID

Method	:	Teflon chambers (6500-7900 l) were filled with dry air (about 5 % relative humidity) at 296±2 K and 987 hPa (indicated as 740 Torr). Methyl nitrite (4-22 · 10E13 molecules cm-3), nitrogen oxide NO (24 · 10E13 molecules cm-3), naphthalene (about 2.1 · 10E13 molecules cm-3), and 1,4-dichlorobenzene as a non-reactive standard, were irradiated with black light lamps for 5-20 minutes. Products were analysed by capillary-GC-FID.
Result	:	Phthalic anhydride was formed from naphthalene with a yield of about 3 % as a naphthalene degradation intermediate
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

11.01.2005 (68)

Type of measurement	:	other: Photooxidation of naphthalene adsorbed on silica gel
Media	:	air
Concentration	:	
Method	:	GC-MS and HPLC-MS
Result	:	15 % of the naphthalene present at the beginning of the irradiation disappeared. About half of the naphthalene which had reacted (48 %) was recovered in the form of reaction products. The yield of phthalic anhydride was 0.1 %.
Test condition	:	Naphthalene together with potassium nitrite (representative for nitrogenous air pollutants) was adsorbed on silica gel and exposed to light from a mercury lamp in a pyrex glass for 5 hours
Reliability	:	(2) valid with restrictions Basic data given
Flag	:	Critical study for SIDS endpoint

11.01.2005 (69)

Type of measurement	:	concentration at contaminated site
Media	:	air
Concentration	:	
Method	:	fractionation by HPLC, analysis by GC/MS
Method	:	- Samples were collected in large fiber bag houses for 18 months (similar to the urban air standard reference material SRM 1648 of the National Bureau of Standards, Washington, DC) - Extraction of 1 g sample by 50 ml toluene for 16 h - Extract dried and redissolved in dichloromethane, filtered - Normal phase HPLC with hexane and dichloromethane - GC (Finnigan 9610, injector temperature 280°C, interface temperatrue 240 °C, column temperature 100- up to 325 °C)/MS (Finnigan 4021, ion source 250 °C, recording of Electron impact chemical ionization [EI] or recording of negative ion chemical ionization [NICI])
Result	:	Phthalic anhydride was detected in urban air particles from St. Louis (MO, USA)
Reliability	:	(4) not assignable Documentation insufficient for assessment
Flag	:	Critical study for SIDS endpoint

29.11.2004 (70)

Type of measurement	:	concentration at contaminated site
Media	:	air
Concentration	:	
Method	:	GC/MS
Method	:	- Samples collected in the suburban Tsukuba area, 60 km NE of Tokyo, on April 28-29, 1985. Aerosol was collected on Pallflex quartz fibre filters - Filter extraction with dichloromethane and methanol, each for 4 h

- Extract dried, redissolved in dichloromethane, thinlayer chromatography
- Esterification of free acids by diazomethane
- GC on Hewlett Packard GC 5840A with OV-1 column (30-300 °C)
- GC/MS with Hewlett Packard GC 5710A GC and JMS DX-300 MS

Remark : Insufficiently documented in regard to phthalic anhydride analysis
Result : Phthalic anhydride and phthalic acid were identified in aerosols collected north of Tokyo in 1985
Reliability : (4) not assignable
Documentation insufficient for assessment
Flag : Critical study for SIDS endpoint
05.10.2005 (71)

Type of measurement : background concentration
Media : air
Concentration :
Method : no data

Remark : EPA notes that the presence of the anhydride could have resulted from the hydrolysis of phthalate esters followed by dehydration in the GC injection port
Result : Phthalic anhydride has been detected in arctic air at the concentration of 10 ng/m3, but it is noted that the presence of the anhydride could have resulted from the hydrolysis of phthalate esters followed by dehydration in the GC injection port
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
28.04.2004 (12)

Type of measurement : background concentration
Media : air
Concentration :
Method : US National Ambient VOC Data Base used, but no other data supplied

Result : Phthalic anhydride is reported to be detected at one location with more than 10 samples. The median phthalic anhydride concentration was less than 6 µg/m3. The half life of phthalic anhydride in air was estimated to be longer than 5 days.
Reliability : (4) not assignable
Secondary literature
Flag : Critical study for SIDS endpoint
29.11.2004 (72)

Type of measurement : concentration at contaminated site
Media : other: aerosol
Concentration :
Method : GC-MS

Method : - Collection of aerosol samples (< 3 µm) for 24 hours every sixth day over one year (1993) in Los Angeles
- Fractionating of the dichloromethane extract by HPLC
- Analysis of the fractions by capillary GC-MS (selected ion monitoring and full-scan modes)

Remark : Phthalic anhydride was not found in total samples, but in subfractions
Result : Phthalic anhydride was tentatively identified in aerosols collected in Los Angeles in 1993. Tentative phthalic anhydride concentrations were reported to be 5.9 mg/kg of extractable organic carbon (EOC). From the annual average of the ambient EOC concentration (8.89 µg/m3), a phthalic anhydride concentration of 52 pg/m3 is calculated for the Los Angeles aerosol
Reliability : (2) valid with restrictions

Basic data given
Flag : Critical study for SIDS endpoint
11.01.2005 (73)

Type of measurement : concentration at contaminated site
Media : air
Concentration :
Method : SPME and GC/MS

Method : - Phthalic anhydride purity > 99 %, obtained from Aldrich, used without further purification
- Air sampling in accordance to CEN TC264/WG62 guideline with evacuated Nalophan (terepthalic ester copolymers) bags (9 l)
- SPME (solid-phase microextraction) with 3 different types of fibres
- GC/MS with Varian 3800 GC, coupled to ion trap mass detector Varian Saturn 2000, samples were desorbed in GC injection port for 3 min at 250 °C
- Substance identification by mass spectra comparison with the NIST(USA)92 library
- Quantification by comparison with deuterated p-xylene and several standard compounds (but not phthalic anhydride)
Remark : Since also phthalic acid diethyl ester was contained in the air samples, it is not excluded that phthalic anhydride was formed in the injector system of the GC
Result : In 4 air samples collected over landfills the concentrations of phthalic anhydride were 0.06 ppb, 0.16 ppb, and 2 samples were below the detection limit of <0.06 ppb. No phthalic anhydride was detected in several air samples of the vicinity of the landfills
Reliability : (4) not assignable
Basic data given
Flag : Critical study for SIDS endpoint
29.11.2004 (74)

Type of measurement : concentration at contaminated site
Media : other: fly ash
Concentration :
Method : GC/MS

Remark : US EPA (1994) noted that the presence of the phthalic anhydride in water could have resulted from the hydrolysis of phthalate esters followed by dehydration in the GC injection port. Thus, the significance of studies using similar GC techniques is rather limited because phthalic anhydride might be formed during these analytical procedures
Result : Phthalic anhydride was identified by comparison with the mass spectrum of the standard compound
Test condition : - Fly ash from an conveyer of an electrostatic precipitator of a municipal solid waste incinerator
- During sample preparation hexane extract is washed with aquatic media
- Isothermic GC at 280 °C using Hewlett Packard 5890A GC, injection port temperature 280 °C
- MS using IMS DX-302/JMA 5100 data system, JEOL, Japan
Test substance : Reagent grade phthalic anhydride from WAKO Pure Chemical Ind. Ltd. Japan
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
29.11.2004 (75)

Type of measurement : concentration at contaminated site
Media : other: exhaust air

Concentration :
Method : GC/MS

Method : - Extraction of exhaust particulate matter by dichloromethane for 24 h and methanol for another 24 h under N2
- Absorption of aliphatics on SiO2 during HPLC with hexane
- GC (Carlo Erba 4160 with FID) on SE-33, injector port up to 80 °C
- Final elution temperature 280 °C
- GC/MS with Hewlett-Packard GC-MSD, ion source 250 °C, analyser 230 °C

Remark : US EPA (1994) noted that the presence of the phthalic anhydride in water could have resulted from the hydrolysis of phthalate esters followed by dehydration in the GC injection port. Thus, the significance of studies using similar GC techniques is rather limited because phthalic anhydride might be formed during these analytical procedures

Result : Phthalic anhydride was present in diesel exhaust particulates

Test substance : Phthalic anhydride purchased from Aldrich (Milwaukee, WI). No purity reported.
The diesel exhaust sample (Standard reference material = SRM) was provided by the Ford Motor Company (Dearborn, MI). It consisted of HPLC fractions of National Bureau of Standards SRM 1650 collected from heat exchangers of different engines operating under a wide varity of conditions

Reliability : (2) valid with restrictions
Basic data given

Flag : Critical study for SIDS endpoint
30.11.2004 (76)

Type of measurement : concentration at contaminated site
Media : other: exhaust air
Concentration :
Method :

Remark : Literature review
Result : Phthalic anhydride is not reported to be present in vehicle exhaust air
Reliability : (4) not assignable
Secondary literature
11.01.2005 (77)

Type of measurement : concentration at contaminated site
Media : other: aqueous oak smoke prepartion
Concentration :
Method : GC/MS

Method : - Oak (Quercus sp.) sawdust (< 2mm) was pyrolyzed at about 370 °C (maximum 557 °C) for about 50 min
- Smoke was filtered to eliminate solids and trapped in water
- Water was neutralized and extracted with dichloromethane (fraction F1). The water was evaporated and the residue dissolved in methanol (fraction F2)
- GC/MS Hewlett-Packard GC 6890 Series II, equipped with MSD 5973. Fused-silica capillary column with HP-5 phenyl methyl silicone, column temperature 50-280 °C, injector at 250 °C, detector at 280 °C
- Identification by GC retention time, mass spectra, and comparison of mass spectra with standard spectra from Wiley 138k Mass Spectra Database
- Quantification with Hewlett-Packard GC 5890 Series II, equipped with flame ionization detector and HP 3395 integrator. Fused-silica capillary column with HP-5 phenyl methyl silicone, column temperature 50-280 °C, Injector at 250 °C, detector at 300 °C

Result : Phthalic anhydride was detected in aqueous oak smoke preparations

(water soluble fraction).
Due to overlapping during GC, phthalic anhydride could not be quantified.
Oak smoke and its aqueous preparations are used in the production of several smoked foods and alcoholic beverages.

Test substance : For phthalic anhydride no standard compound was used; identification see Method
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
30.11.2004 (78)

Type of measurement : concentration at contaminated site
Media : other: extracts of weathered sandstone surfaces
Concentration :
Method : GC/MS

Method : - Soxhlet extraction for 14 h with hexane/ethylacetate or extraction with water in flask shaken for 2 h
- GC: Varian 3400, injector at 250 °C, BP5 column
- MS: Finnigan MAT 95, transfer line at 250 °C
Remark : Phthalic acid and phthalates were also present in the extracts. Since the injector for the GC was held at 250 °C, formation of phthalic anhydride from these compounds cannot be excluded.
Result : Phthalic anhydride is also reported to occur in the organic compounds extracted from weathered surfaces of Saxonean sandstone from historic buildings in the city of Dresden, Germany (Machill et al., 1997). Potential sources of phthalic anhydride include microorganisms in these surfaces, but -although not discussed in detail - the more likely source being deposition of air contaminants. Phthalic acid and phthalates were also present in the extracts. Since the injector for the GC was held at 250 °C, formation of phthalic anhydride from these compounds cannot be excluded.
Reliability : (4) not assignable
Documentation insufficient for assessment
Flag : Critical study for SIDS endpoint
17.05.2004 (79)

Type of measurement : concentration at contaminated site
Media : air
Concentration :
Method : GC/MS

Method : - 3 commercially available hydrocarbon based coating materials for interior wood surfaces tested
- GC with Hewlett Packard 5890 GC equipped with DB-5 capillary column, 10-240 °C, ATD 400 as the detector
- MS with Hewlett Packard 5989 mass spectrometer
- Identification by comparison of mass spectra with that of standard MS library (NBS75K)
- Quantification from GC peak area assuming that all compounds have equal response to the detector
Remark : No measures were reported to avoid formation of phthalic anhydride during analysis (GC-MS). Injector temperature not reported but presumably higher than 240 °C. Many compounds not (completely) identified.
Result : Phthalic anhydride was reported to be a trace component in the emissions from hydrocarbon based wood stains for indoor materials (0-2 mg/g of ready-to-use wood stain)
Reliability : (4) not assignable
Documentation insufficient for assessment
Flag : Critical study for SIDS endpoint
17.05.2004 (80)

Type of measurement : concentration at contaminated site
Media : air
Concentration :
Method : HPLC, GC/MS

Result : Phthalic anhydride was detected as a thermolytic degradation product of 5 out of 11 analyzed steel protective paint. Steel plates coated with primer or finishing paint yielded up to 0.88 g phthalic anhydride/m3 upon heating at 350 °C
Test condition : - Sampling with filters, adsorption tubes and bubbler absorbers (recomended: XAD-2 tube with preconnected glass fiber filter and a chemosorbent tube)
- Coated steel plates (170 x 500 x 5 mm) were heated to 350 °C for 7 min with a gas flame
- Several coatings examined: Epoxy, ethylsilicate, PVB, chlororubber, alkyd and specials
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
30.11.2004 (81)

Type of measurement : background concentration
Media : drinking water
Concentration :
Method : no data

Remark : US EPA (1994) noted that the presence of the phthalic anhydride in water could have resulted from the hydrolysis of phthalate esters followed by dehydration in the GC injection port. Thus, the significance of studies using similar GC techniques is rather limited because phthalic anhydride might be formed during these analytical procedures
Result : The porpuse of the study is to support the establishment of an US register of organic pollutants in water. It is reported that phthalic anhydride was detected in 2 industrial effluents and in 4 drinking water samples. Neither a source nor a method for these data is supplied.
Reliability : (4) not assignable
Documentation insufficient for assessment
07.10.2005 (82)

Type of measurement : concentration at contaminated site
Media : air
Concentration : .004 - .203 µg/l
Method : HPLC according to NIOSH Method S-179

Remark : NIOSH (1980) study is cited on potentially exposed US workers. In 1972-1974 approximately 142000 workers were potentially exposed to phthalic anhydride in the USA (NIOSH (1980), National Occupational Hazards Survey, 1972-1974. Cincinnati, OH (Updated as of August 1980))
Result : In an US factory manufacturing phthalic anhydride, di(2-ehtylhexyl)phthalate, and other phthalates, the air concentrations of phthalic anhydride were 4 - 203 µg/m3 (mean 11 - 79 µg/m3) in manufacturing, storage, and processing workplace areas
Test condition : - Air sampling during workshift with personal sampling pump, 1 l/min
- Absorption on Millipore AA filters (37 mm diameter)
- Limit of detection 1.5 µ/sample
Reliability : (4) not assignable
Documentation insufficient for assessment
28.10.2005 (83)

Type of measurement : concentration at contaminated site

Media : air
Concentration : < .1 - 13 µg/l
Method : HPLC with UV-detection

Result : In 2 alkyd and/or saturated polyester resin plants, time-weighted average concentrations of phthalic anhydride dust were 2.8 and 4.9 mg/m3 during manual loading of reactors from paper bags, 6.1 and 13 mg/m3 during handling of emptied paper bags, and <0.3 and 0.3 mg/m3 during cleaning, respectively. In one of the plants, also the dust concentration was determined during general work (including sampling from reactor, 0.15 mg/m3) and in the canteen (< 0.1 mg/m3). 40 - 46 % of the dust was in the respirable dust fraction
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
21.10.2005 (84)

Type of measurement : concentration at contaminated site
Media : air
Concentration : 1.5 - 17 µg/l
Method : HPLC

Result : In alkyd and/or saturated polyester resin plants, working place air concentrations of phthalic anhydride were 6.6 mg/m3 (range 1.5 - 17 mg/m3) during phthalic anhydride loading of reactors
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
21.10.2005 (85)

Type of measurement : concentration at contaminated site
Media : air
Concentration : < .00002 - .005 µg/l
Method : GC with EC detection

Result : In 6 PVC plastics processing plants using PVC containing organic phthalates as plasticizers, the workplace air concentrations of phthalic anhydride (and DEHP in 9 plants) were determined (Vainiotalo and Pfaeffli, 1990). Phthalic anhydride levels ranged from below the detection limit (<0.02 µg/m3) to 5 µg/m3. For comparison, the phthalate levels were up to 100 times higher (< 0.02 - 0.5 mg/m3). Use of heat sealers may therefore expose users of PVC film to phthalic anhydride (SRC, 1995).
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
21.10.2005 (86) (50)

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

3.3.2 DISTRIBUTION

Media : water - air
Method : other (calculation): HENRYWIN v. 3.10

Year : 2004

Remark : The calculated value reflects the properties of the unhydrolyzed molecule without taking into account the sensitivity of phthalic anhydride towards hydrolysis
Result : Henry's law constant:
Bond method: 0.64 Pa m³ mole-1
Test substance : Phthalic anhydride
Reliability : (2) valid with restrictions
Accepted calculation method
Flag : Critical study for SIDS endpoint
06.10.2005 (39)

Media : water - air
Method : other (calculation): HENRYWIN v. 3.10
Year : 2004

Remark : Phthalic acid is the major organic degradation product of phthalic anhydride hydrolysis
Result : Henry's law constant:
Bond method: 2.21*10E-07 Pa m³ mole-1
Test substance : Phthalic acid
Reliability : (2) valid with restrictions
Accepted calculation method
Flag : Critical study for SIDS endpoint
29.07.2004 (40)

Media : water - air
Method : other (calculation):
Year : 2001

Method : Estimation according to the RCRA Support Documentation hierarchy for preliminary screening (USEPA)
Result : Henry's law constant:
0.002 Pa m³ mole-1
Test substance : Phthalic anhydride
Reliability : (2) valid with restrictions
Accepted calculation method
23.07.2004 (87) (88)

Media : water - air
Method : other (calculation)
Year : 1991

Method : Saturated vapour concentration (SVC) was calculated with the molecular weight and the vapour pressure from the TLV (Threshold limit value) document and set in relation to the TLV value to check whether measurements on either vapour or aerosol phase alone would correctly monitor the exposure of workers at the work place
Result : The relation SVC/TLV was about 70 indicating that even at a relative humidity of 99 %, less than 5 % of the substance in the atmosphere is adsorbed to the particle phase
Reliability : (2) valid with restrictions
Basic data given
06.10.2005 (89)

Media : other: air - biota - sediment(s) - soil - water - aerosol
Method : Calculation according Mackay, Level I
Year : 2004

Method : Chemical data used for the calculation:
- Temperature (°C) = 25
- Molar mass (g/mol) = 148.12
- Vapour pressure (Pa) = 0.06
- Water solubility (g/m³)= 16400
- log Kow = 1.6
- Melting point = 131.6°C

Phase properties and composition of the compartments:

	Volumina (m3)	Density (kg/m3)	Organic Carbon (%)
Air:	6.0 E+09	1.185	
Water:	7.0 E+06	1000	
Soil:	4.5 E+04	1500	2
Sediment:	2.1 E+04	1300	5
Susp. Sed.:	3.5 E+01	1500	16.7
Aerosol:	1.2 E-01	1500	
Aquatic Biota:	7.0 E+00	1000	5 (lipid content)

Calculation was performed according to the model described in the first publication of Mackay (1991). Phase properties and composition of the compartments were modified as suggested by the Federal Environmental Agency (UBA, Germany).

Remark : The calculated value reflects the properties of the unhydrolyzed molecule without taking into account the sensitivity of phthalic anhydride towards hydrolysis

Result : Based on the model calculations (Mackay level I, v 2.11) the target compartment of the environmental distribution of phthalic anhydride is the hydrosphere.

Water:	99.35 %
Air:	0.019 %
Sediment:	0.32 %
Soil:	0.32 %
Susp. Sed.:	0.002 %
Aerosol:	<0.001 %
Aquatic Biota:	<0.001 %

Test substance : Phthalic anhydride

Reliability : (2) valid with restrictions
Accepted calculation method

Flag : Critical study for SIDS endpoint

30.11.2004 (39)

Media : other: air - biota - sediment(s) - soil - water - aerosol

Method : Calculation according Mackay, Level I

Year : 2004

Method : Chemical data used for the calculation:
- Temperature (°C) = 25
- Molar mass (g/mol) = 166.13
- Vapour pressure (Pa) = 8.48E-05 (MPBPWIN v1.41, calc.) Water solubility (g/m³) = 7010 (WSKOW v1.41, exp. data from database)
- log Kow = 0.73 (Hansch, 1995)
- Melting point = 191°C (http://toxnet.nlm.nih.gov/cgi-bin/sis/search/f?./temp/~8hISkI:1, 2004)

Phase properties and composition of the compartments:

	Volumina (m3)	Density (kg/m3)	Organic Carbon (%)

Air:	6.0 E+09	1.185	
Water:	7.0 E+06	1000	
Soil:	4.5 E+04	1500	2
Sediment:	2.1 E+04	1300	5
Susp. Sed.:	3.5 E+01	1500	16.7
Aerosol:	1.2 E-01	1500	
Aquatic Biota:	7.0 E+00	1000	5 (lipid content)

Calculation was performed according to the model described in the first publication of Mackay (1991). Phase properties and composition of the compartments were modified as suggested by the Federal Environmental Agency (UBA, Germany).

Remark : Phthalic acid is the major organic degradation product of phthalic anhydride hydrolysis

Result : Based on the model calculations (Mackay level I, v 2.11) the target compartment of the environmental distribution of phthalic acid is the hydrosphere.

Water:	99.91 %
Air:	<0.001 %
Sediment:	0.043 %
Soil:	0.042 %
Susp. Sed.:	<0.001 %
Aerosol:	<0.001 %
Aquatic Biota:	<0.001 %

Test substance : Phthalic acid

Reliability : (2) valid with restrictions
Accepted calculation method

Flag : Critical study for SIDS endpoint

30.11.2004 (40)

Media : water - soil

Method : other (measurement): modified OECD-Guideline 106

Year : 1991

Remark : The sorption equilibrium was reached within 16 hours. The mass balance resulted in a recovery of > 80 %.

Result : Sorption coefficient Koc determined for different soils:

- Podzol : 31
- Alfisol (agricultural soil): 2
- sediment (Lake Constance) : 2

Test condition : - Soils:
three different soils like acidic forest soil, Podzol and agricultural soil and a sublimnic soil
- Preparation of the soils:
according to the publication of von Oepen (1989) Chemosphere 18, 1495-1511
- Test procedure:
50 ml test solution with 10 g (dry weight) of the specific soil; soil samples shaken for 0.5, 1, 1.5, 5, 24 and 72 h;
the concentration of the test substance in an aliquot of 1 ml of the water-phase was tested
- Adsorption:
incubation period 16 hours; initial concentration 15, 0.5, and 0.15 mg/l; replicate (one control, one blank)
- Analysis:
GC, HPLC

Test substance : Phthalic acid, purity not specified

Reliability : (1) valid without restriction
Reliable without restrictions
Flag : Critical study for SIDS endpoint
22.07.2004 (90)

Media : water - soil
Method : other (calculation): PCKOCWIN v1.66 (2000)
Year : 2004

Remark : The calculated value reflects the properties of the unhydrolyzed molecule without taking into account the sensitivity of phthalic anhydride towards hydrolysis
Result : Koc = 10.84
Test substance : Phthalic anhydride
Reliability : (2) valid with restrictions
Accepted calculation method
Flag : Critical study for SIDS endpoint
29.07.2004 (39)

Media : water - soil
Method : other (calculation): PCKOCWIN v1.66 (2000)
Year : 2004

Remark : Phthalic acid is the major organic degradation product of phthalic anhydride hydrolysis
Result : Koc = 73.06
Test substance : Phthalic acid
Reliability : (2) valid with restrictions
Accepted calculation method
Flag : Critical study for SIDS endpoint
29.07.2004 (40)

Media : water - soil
Method :
Year : 1980

Method : Using equations of Kenaga EE and Goering CAI (1980) Relationship between Water Solubility, Soil Sorption, Octanol-Water Partitioning and Bioconcentration of Chemicals in Biota. Aquatic Toxicology ASTM STP 707 ((J. C. Eaton, P. R. Parrish and A. C. Hendriks, Eds.), American Society for Testing and Materials, in Press)
Result : Koc = 36
Test substance : Phthalic anhydride
Reliability : (4) not assignable
Secondary literature
21.07.2004 (91)

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic
Inoculum : activated sludge
Concentration : 100 mg/l related to Test substance
related to
Contact time :
Degradation : 85.2 (±) % after 14 day(s)

Result	:	readily biodegradable
Deg. product	:	
Method	:	other: Japanese Guideline by MITI (1974). Comparable to OECD TG 301 C, Modified MITI Test I
Year	:	1992
GLP	:	no data
Test substance	:	other TS: phthalic anhydride, purity is not specified
Method	:	The test was conducted in accordance with 'Biodegradation test of chemical substance by microorganisms etc.' stipulated in the Order Prescribing the Items of the Test Relating to the New Chemical Substance (1974, Order of the Prime Minister, the Minister of Health and Welfare, the Minister of International Trade and Industry No.1). This guideline corresponds to '301C, Ready Biodegradability: Modified MITI Test I' stipulated in the OECD Guidelines for Testing of Chemicals (1981)
Test condition	:	Sludge concentration: 30 mg/l
Reliability	:	(2) valid with restrictions Guideline study with acceptable restrictions
Flag	:	Critical study for SIDS endpoint

15.06.2004 (24)

Type	:	aerobic
Inoculum	:	activated sludge
Concentration	:	100 mg/l related to Test substance related to
Deg. product	:	
Method	:	other: Japanese Guideline by MITI (1974). Comparable to OECD TG 301 C, Modified MITI Test I
Year	:	1978
GLP	:	no
Test substance	:	other TS: phthalic anhydride, purity is not specified
Remark	:	Well-biodegradable is, if the percentage biodegradation from the oxygen consumption exceeds >= 30 % after 2 weeks from beginning of the test (result of a direct analysis)
Result	:	Phthalic anhydride is confirmed to be well-biodegradable.
Test condition	:	- sludge concentration: 30 ppm (to 100 ppm test substance) - temperature: 25 +/- 2 °C - pH of supernatant of active sludge: 7.0 +/- 1 - test period: 14 days - reference substance: aniline
Reliability	:	(2) valid with restrictions Guideline study with acceptable restrictions
Flag	:	Critical study for SIDS endpoint

15.07.2004 (92)

Type	:	aerobic
Inoculum	:	activated sludge, industrial, adapted
Contact time	:	24 hour(s)
Degradation	:	33 (±) % after 24 hour(s)
Result	:	
Kinetic of testsubst.	:	0 hour(s) 0 % 2 hour(s) 22 % 4 hour(s) 22 % 24 hour(s) 33 % %
Deg. product	:	
Method	:	other: "fill and draw" batch system

Year : 1975
GLP : no
Test substance : other TS: phthalic anhydride, purity is not specified

Remark : Related to COD(Mn)
Result : Kinetic of TOC removal efficiency (%):
0 h: 0
2 h: 23
4 h: 35
24 h: 88
(detected with TOC-analyzer, Model 102 from Beckman Toshiba Ltd.)
Test condition : - Activated sludge was taken from the Kashima Petroleum and Petrochemical Complex in Japan
- It was assumed, that the activated sludge was well acclimated to organic substances
- Temperature: 25 °C
- pH-values of test solutions were well controlled during the test
- The used apparatus was a fill-and-draw type unit, one with two aeration cylinders of 7 l, the other with two aeration cylinders of 30 l
- Air supply: 5 l/min
- Aeration conditions:
MLVSS (Mixed Liquor Volatile Suspended Solid): 2660 ppm
SVI (Slugde Volume Index): 12 ml/g
- The method used to determine COD(Mn) was formulated in the Japanese Industrial Standard - JIS K0102.
Reliability : (2) valid with restrictions
Test procedure in accordance with generally accepted scientific principles and described in sufficient detail
Flag : Critical study for SIDS endpoint
30.11.2004 (93) (55)

Type : aerobic
Inoculum : activated sludge, industrial, adapted
Concentration : 65 mg/l related to Test substance
related to
Contact time :
Degradation : 88 (±) % after 1 day(s)
Result :
Deg. product :
Method : other: "fill and draw" batch system
Year : 1988
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Method : COD was determined using Japanese Industrial Standard Methods (JIS K0102).
TOC was measured using a TOC analyser (Shimadzu TOC-10B).
Remark : Acclimatization period: 1 day
Result : Degradation:
33 % related to COD removal,
88 % related to TOC removal
Test condition : - Activated sludge was taken from the Fukashiba wastewater treatment plant of the Kashima Petrochemical Complex in Japan.
- Concentration of the water samples was between 100 and 200 mg/l in terms of COD or about 100 mg/l in terms of the concentration of the test substance
- 2.0 l of the sample water were added to 0.5 l of activated sludge and aeration of the mixed liquor was started.
- After 23 h aeration and 1 h sedimentation 2.0 l of the supernantant solution were replaced by the sample water. The fill and draw system was

therefore used to acclimatize the sludge to the test water.
- After acclimatization the water in the container was sampled during aeration at the beginning (0 h) and 24 h later for analysis.
- The oxygen uptake and the decreases in TOC and COD after cultivation were measured and the biological degradability calculated.
- The conditions in the aeration container were:
MLSS (mixed liquor suspended solids) 2000-3000 mg/l, air flow rate about 150 ml/min, water temperature = 25-30 °C.
- pH-value was adjusted to neutral; and both nitrogen and phosphorus were added at 1.3 and 28 mg/l respectively. The salt concentration of the water samples was adjusted to a chloride ion concentration of about 5000 mg/l (same level as that of the wastewater entering the Fukashiba plant).

Reliability : (2) valid with restrictions
Test procedure in accordance with generally accepted scientific principles and described in sufficient detail

Flag : Critical study for SIDS endpoint

22.07.2004 (56)

Type : aerobic
Inoculum : predominantly domestic sewage
Concentration : 3 mg/l related to Test substance
related to
Contact time :
Degradation : 71 (±) % after 30 day(s)
Result :
Kinetic of testsubst. : 5 day(s) 45 %
10 day(s) 58 %
20 day(s) 71 %
30 day(s) 71 %
%
Deg. product :
Method : OECD Guide-line 301 D "Ready Biodegradability: Closed Bottle Test"
Year : 1972
GLP : no
Test substance : other TS: phthalic anhydride, purity is not specified

Test condition : Initial concentration of test substance 1000 mg/l (COD of stock solution is 1584 mg/l)

Reliability : (2) valid with restrictions
Basic data given

Flag : Critical study for SIDS endpoint

22.07.2004 (94)

Type : aerobic
Inoculum : predominantly domestic sewage
Concentration : 3 mg/l related to Test substance
related to
Contact time :
Degradation : 74 (±) % after 30 day(s)
Result :
Kinetic of testsubst. : 5 day(s) 48 %
10 day(s) 68 %
20 day(s) 64 %
30 day(s) 74 %
%
Deg. product :
Method : OECD Guide-line 301 D "Ready Biodegradability: Closed Bottle Test"
Year : 1973
GLP : no
Test substance : other TS: phthalic acid, purity not specified

Test condition	:	Initial concentration of test substance 1000 mg/l (COD of stock solution is 1600 mg/g)
Reliability	:	(2) valid with restrictions Basic data given
Flag	:	Critical study for SIDS endpoint

22.07.2004 (95)

Type	:	aerobic
Inoculum	:	
Deg. product	:	
Method	:	
Year	:	1974
GLP	:	no
Test substance	:	other TS: Phthalic anhydride, purity is not specified
Deg. products	:	124-38-9 204-696-9 carbon dioxide 88-99-3 201-873-2 phthalic acid
Remark	:	Phthalic anhydride was one of 20 organic compounds chosen to investigate its environmental fate including metabolism in the food-chains, degradative pathways, bioaccumulation, ecological magnification (E.M.) and biodegradability index (B.I.)
Result	:	The B.I. of phthalic acid is 11.884.
Test condition	:	The model aquatic ecosystem consists of a 3-liter flask, which contains reference standard water and food chain members. The whole system is kept in a programmed growth chamber with constant air flow, temperature and photoperiod.
Conclusion	:	Phthalic anhydride is readily biodegradable and not a micropollutant. The major degradation pathway was hydrolysis, followed by decarboxylation. Conjugation with the acidic proton was the most important degradation pathway as reflected by high BI values (Lu and Metcalf 1975, see also Chapter 3.7 of this IUCLID: Bioaccumulation).
Reliability	:	(3) invalid Unsuitable test system

06.10.2005 (96) (22)

Type	:	anaerobic
Inoculum	:	other bacteria: two cultures of bacteria (termed ON-7 and MO), adapted
Deg. product	:	
Method	:	other: miscellanous, see below
Year	:	1981
GLP	:	no data
Test substance	:	other TS: phthalic acid, purity is not specified
Method	:	- Cultural methods: Incubation at 30°C in 18-ml screw cap tubes filled with medium. Phthalic acids were added and agar. Batch cultures were grown either anaerobically in screw cap bottles filles with medium or aerobically in Erlenmeyer flasks containing medium. - Respirometry: Aerobic respiration was measured at 30°C either manometrically or polarographically. Substrate was added after endogenous activity. In anaerobic incubations, the test item was added under anaerobic conditions at zero time. CO2 production was measured by ommiting KOH at the end of the experiment. - Chromatography: Aqueous samples were acidified and extracted for analysis by thin-layer chromatography or gas-liquid chromatography. - Other methods: Standard tests for bactarial identification and miscellanous unsuitable test systems.
Remark	:	Bacteria obtained from the marine sediments of Biscayne Bay.
Result	:	Denitrifing, mixed cultures of bacteria which grew anaerobically with denitrification on phthalic acid were enriched and maintained. Two cultures,

termed ON-7 and MO, were studied in detail.

Under aerobic conditions both cultures seemed to metabolize phthalic acid via protocatechuate. Anaerobically grown cells of culture ON-7 rapidly metabolized phthalic acid.

Reliability : (3) invalid
Unsuitable test system

22.07.2004 (97) (98)

Type : aerobic
Inoculum :
Deg. product :
Method : other: calculated ba QSAR models
Year : 2001
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Remark : Multiple linear regression (MLR) and artificial neural network (ANN) models were presented to predict the biodegradability. The biodegradation data of a diverse set of 241 molecules were divided into a training set of 172 chemicals for developing the MLR and ANN models and into test sets of 12 and 57 chemicals for evaluating the predictive ability of these models. Parameters used for establishing the models were molecular connectivity (1 parameter) and 14 atom-type E-stat indices. The linear model revealed a square correlation coefficient (r^2) of 0.76 for the training set and a r^2 of 0.68 for the test set. Better predictions were achieved for the artificial neural network resulting in a square correlation coefficient of 0.84 for the training set and 0.76 for the test set, respectively.
Both models predicted a fast biodegradation of phthalic anhydride belonging to the second test set. This result was confirmed by the observed biodegradability of phthalic anhydride reported in this paper as "biodegrades rapidly" (inherently).

Conclusion : Development of QSAR correlation: correlation coefficient < 0.8; observed results are second quotations not assignable to the origin

Reliability : (4) not assignable
Not assignable

30.11.2004 (99)

Type :
Inoculum : activated sludge, domestic, non-adapted
Concentration : 10 mg/l related to Test substance
related to
Contact time :
Degradation : 99 (±) % after 14 day(s)
Result :
Deg. product :
Method : OECD Guide-line 301 E "Ready biodegradability: Modified OECD Screening Test"
Year :
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Reliability : (4) not assignable
Secondary literature

06.10.2005 (100)

Type : aerobic
Inoculum : other: activated sludge (flowing off) of sewage plant Marl-Ost
Concentration : 20 mg/l related to DOC (Dissolved Organic Carbon)
related to

Contact time	:	
Degradation	:	99 (±) % after 5 day(s)
Result	:	
Deg. product	:	
Method	:	OECD Guide-line 301 E "Ready biodegradability: Modified OECD Screening Test"
Year	:	1983
GLP	:	no data
Test substance	:	other TS: phthalic anhydride, purity is not specified
Remark	:	- Concentration of stock solution: 535 mg/l DOC, - TOC-analyzer: Beckmann - All DOC-values were determined after membrane infiltration (Sartorius no. 11307) and threetimes scald out for 1 hour with water to deliver from detergens
Reliability	:	(4) not assignable Secondary literature

06.10.2005 (101)

3.6 BOD5, COD OR BOD5/COD RATIO

BOD5		
Method	:	other: Standard Dilution Method
Year	:	1950
Concentration	:	related to
BOD5	:	1190 mg/l
GLP	:	no
Method	:	- Testconcentration 0.5 g/l - pH 7 - 8.5 (if required neutralisation with 50 % NaOH) - Four to eight dilutions on all samples in duplicate - Temperature 20 °C - dilution water for BOD: mixed with domestic sewage (2.2 ml (50cc.) settled sewage per l (5 gallons) dilution water) for COD: synthetic dilution water as described in the Ninth Edition of "Standard Methods for the Examination of Water and Sewage"
Result	:	BOD5 : 73 % ThOD, ThOD = 1620 g/g.
Test substance	:	Phthalic anhydride, purity not specified
Conclusion	:	Phthalic anhydride could not hinder biological sewage treatment in this study.
Reliability	:	(2) valid with restrictions Basic data given

23.07.2004 (102)

BOD5		
Method	:	other: Standard Dilution Method
Year	:	1955
Concentration	:	related to
BOD5	:	720 mg/l
GLP	:	no
Result	:	BOD5 - values (20 °C) listet in Verschueren: 44 % related to ThOD 74 % related to ThOD 78 % related to ThOD (conc. 1 - 4 ppm) ThOD = 1.62 g/g

Source	:	The biodegradation data were determined by: - Hess RW, Private Communication - Jones HR (1971) Environmental control in the organic and petrochemical industries "Noyes Data Corporation"
Test condition	:	Temperature 20 °C
Test substance	:	Phthalic anhydride, purity not specified
Reliability	:	(4) not assignable Documentation insufficient for assessment

30.11.2004 (103) (28)

BOD5		
Method	:	other
Year	:	1981
Concentration	:	2 mg/l related to Test substance
BOD5	:	mg/l
GLP	:	no
Method	:	Standard dilution method (S.D.M.) and Sea water dilution method (S.W.D.M.)
Result	:	Degradation (%) of an initial concentration of 2 ppm according to the standard dilution (SDM) and sea water dilution method (SWDM) after 5 days: SDM : 21 (BOD 0.346 g/g) SWDM: 18 (BOD 0.288 g/g) (ThOD 1.62 g/g)
Source	:	Only abstract and chemical names in english available
Test substance	:	Phthalic anhydride, purity not specified
Reliability	:	(4) not assignable Original reference in Japanese and not translated

30.11.2004 (104)

3.7 BIOACCUMULATION

BCF	:	3.4
Elimination	:	
Method	:	other: (calculated) SRC-BCFWIN v2.15
Year	:	2004
GLP	:	no
Test substance	:	other TS: phthalic anhydride
Remark	:	The calculated value reflects the properties of the unhydrolyzed molecule without taking into account the sensitivity of phthalic anhydride towards hydrolysis
Reliability	:	(2) valid with restrictions Accepted calculation method
Flag	:	Critical study for SIDS endpoint

29.07.2004 (39)

Species	:	
Exposure period	:	at 25 °C
Concentration	:	
BCF	:	3.16
Elimination	:	
Method	:	other: (calculated) SRC-BCFWIN v2.15
Year	:	2004

GLP : no
Test substance : other TS: phthalic acid

Remark : Phthalic acid is the major organic degradation product of phthalic anhydride hydrolysis
Reliability : (2) valid with restrictions
Accepted calculation method
Flag : Critical study for SIDS endpoint
22.07.2004 (40)

Elimination :
Method : other: Greenhouse study with 14C-phthalic acid
Year : 1985
GLP : no
Test substance : other TS: label 14C = 0 (Amersham CFA 766 Batch 5)

Method : Plant uptake and soil retention of 14C carboxyl-labelled phthalic acid were studied.
Result : Bioaccumulation factor (BF) [ppm in plant tissue/ppm initial soil application (dry weight basis)] averaged for all tested plants and seeds:
plant : 0.013
seed : 0.0046

Extractable 14C phthalic acid (%) after final harvest:
corn : 4.5
fescue : 5.2
mature wheat : 9.2
wheat seed : 46.7
mature soybean plants: 15.3

Average bioaccumulation ratios for total 14C:
- for seeds : 0.0005
- for plants : 0.003

Test condition : - Test system:
14C-labelled phthalic acid added to unlabelled phthalic acid, dissolved in ethanol and mixed into the upper 15 cm (5.8 kg) of the soil in each pot (6400 dpm/g of dry weight soil)
- Application rate:
0.6, 6.0, 60.0 and 600.0 ppm
- Application time in soil:
4 days
- Testorganism:
after the application time of 4 days 25 wheat seeds, 10 corn seeds, 15 soybeans, 2.5 cm^3 of tall fescue were planted in each pot; three replicates
- Harvest
corn and fescue plants at 21 and 45 days after final planting, soybean and wheat when mature at 74 days,
- Analysis:
liquid scintillation spectrometer (Packard TRi-Carb Model 2405)
Test substance : Specific activity 60 mCi/mmol
Reliability : (2) valid with restrictions
Study well documented
Flag : Critical study for SIDS endpoint
03.08.2004 (105)

Species : other: Oedogonium cardiacum (green algae)
Exposure period : 48 hour(s) at 26.7 °C
Concentration :
BCF : 3169
Elimination :

Method	:	other: Model aquatic system
Year	:	1975
GLP	:	no
Test substance	:	other TS: phthalic anhydride; label 14C = 0 (New England Nuclear)
Remark	:	Phthalic anhydride was almost quantitatively converted to phthalic acid and thus underwent further metabolic reactions. Alga was the only ecosystem component that stored the parent compound to high levels, i.e., EM 3169. Phthalic acid was magnified to 200. A substantial amount of 14CO2, 5.02% of total applied radioactivity, was collected over 3-day period. Thus decarboxylation occured as a major degradation pathway. Conjugation with the acidic proton was the most important degradation pathway as reflected by the high BI (biodegradability index) values: - 1.779 in alga - 2.411 in mosquito larva - 4.869 in snail - 11.844 in fish - 15.488 in daphnia
Result	:	The EM (Ecological magnification) is equalized to the BCF. But there is no documentation how the EM was dertermined from the measured test results.
Test condition	:	The model aquatic ecosystem consists of a 3-liter flask, which contains reference standard water and food chain members. The whole system is kept in a programmed growth chamber with constant air flow, temperature and photoperiod. - Analytical monitoring: TLC (Thin Layer Chromatography) and Autoradiography - 0.01 - 0.1 ppm of radiolabeled compound (14C) - 12 h daylight to 7500 Lux - Temperature (26.7 +/- 2 °C) - 24 hour test period
Reliability	:	(3) invalid Unsuitable test system

21.07.2004 (22)

3.8 ADDITIONAL REMARKS

22.07.2004

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	semistatic
Species	:	Brachydanio rerio (Fish, fresh water)
Exposure period	:	7 day(s)
Unit	:	mg/l
LC50	:	560
Limit test	:	
Analytical monitoring	:	no data
Method	:	other: according to OECD Guideline Draft "Early Life Stage"
Year	:	1990
GLP	:	no data
Test substance	:	other TS: phthalic anhydride, purity 98 % (FA Merck)
Remark	:	Accepted new scientific name for Brachydanio rerio: Danio rerio
Result	:	LOEC (mortality): 1000 mg/l LOEC (total embryotoxicity): 1000 mg/l EC50 (total embryotoxicity): 561 mg/l
Test condition	:	- Fertilized eggs in the blastula stage (2 - 4 h after spawning); disinfected for 1 min in a 0.04 % formalin solution - test medium: aerated reconstituted water - Solvent: DMSO < 100 µl/l - Photoperiod: 12 h - Temperature: 25 +/-1 °C - pH-value: 8.4 +/- 0.2 - Hardness: 250 mg/l (as CaCO3) - O2-conc.: 8.1 +/- 0.2 - malformed fish determined under a binocular (amplification 30x)
Reliability	:	(2) valid with restrictions Basic data given
Flag	:	Critical study for SIDS endpoint

21.07.2004 (106)

Type	:	semistatic
Species	:	Cyprinus carpio (Fish, fresh water)
Exposure period	:	48 hour(s)
Unit	:	mg/l
LC50	:	> 500
Limit test	:	
Analytical monitoring	:	no
Method	:	other: "Acute Toxicity Test"
Year	:	1996
GLP	:	no
Test substance	:	other TS: Phthalic acid, purity is not specified
Method	:	Descriptions of test procedure have appeared in: Zhao YH, Wang Ls, Gao H, and Zhang Z (1993). Quantitative structure-activity relationships - relationshop between toxicity of organic chemicals to fish and to Photobacterium phosphoreum. Chemosphere 2, 1971-1979.
Result	:	The result is given in log (1/LC50) < 2.52 mol/l. The corresponding LC50 is > 500 mg/l. It is noted that "no concentration with more than 50% inhibition could be tested"
Test condition	:	- Stock solutions of organic test chemicals were prepared in acetone - Test fishes were purchased from a commercial source - Fish were kept under laboratory conditions for more than 2 weeks - Weight of the fish: ca. 5 g

- Length of the fish: 5 cm
- Stock solution were prepared in acetone
- Water renewal all 12 h
- 10 fish in 16 l of test water
- Temperature maintained at 20 +/- 1 °C
- pH 7, test solution was always regulated to pH = 7.8 +/- 0.1, determination at the beginning and end of each test
- Range of exposure concentration (5 concentrations): 50-500 mg/l

Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
26.10.2005 (107) (108)

Type : static
Species : other: Petromyzon marinus (marine fish)
Exposure period : 24 hour(s)
Unit : mg/l
LC0 : >= 5
Limit test :
Analytical monitoring : no
Method : other: Screening Test "Acute Toxicity Test"
Year : 1957
GLP : no
Test substance : other TS: phthalic anhydride, purity is not specified

Method : Screening test
Result : Effects were observed at 5 hours test duration
Test condition : - initial concentration of the test substance 5 ppm
- just one concentration was tested (5 mg/l)
- 2 specimens (larvae) were used, which were collected in the Ocqueoc River (Michigan)
- length of fish was about 10 cm
- test animals were placed in a 10 l glass jar containing varied resultant volumes from 5.8 to 6.2 l
- jar was aerated (at near oxygen saturation)
- oxygen dissolved varied from 8.6 - 13.7 ppm
- free CO2 varied from 5.0 - 9.0 ppm
- water used was drawn from a supply from Hammond Bay of Lake Huron
- water Temperature 12.2 - 13.3 °C (55 +/- 1 degree F)
- pH varied from 7.5 - 8.2
- observations were made approx. six times, at various intervals, during the 24-hour test period

Reliability : (3) invalid
Unsuitable test system. No standard organisms and method were used for the assessment of chemicals
23.07.2004 (109)

Type : static
Species : Leuciscus idus (Fish, fresh water)
Exposure period : 48 hour(s)
Unit : mg/l
LC0 : 100
LC100 : 200
Limit test :
Analytical monitoring : no data
Method : other: Bestimmung der akuten Wirkung von Stoffen auf Fische. Working group "Fischtest im Hauptausschuß Detergenzien" (1973)
Year : 1973
GLP : no
Test substance : other TS: phthalic anhydride, purity is not specified

Remark	:	Direct weight, related to test substance Only two fishes were tested
Reliability	:	(4) not assignable Documentation insufficient for assessment
23.07.2004		(110) (28)
Type	:	static
Species	:	Leuciscus idus (Fish, fresh water)
Exposure period	:	48 hour(s)
Unit	:	mg/l
LC0	:	250
LC50	:	313
LC100	:	360
	:	0
Limit test	:	
Analytical monitoring	:	no data
Method	:	other: DIN-Standard 38412 L15 (Fish short-time test)
Year	:	1982
GLP	:	no data
Test substance	:	other TS: phthalic anhydride, purity is not specified
Method	:	Method of the German Standards Institution Berlin, Germany
Remark	:	Test procedure according to national standard method
Reliability	:	(4) not assignable Original reference not available
25.11.2004		(111)
Type	:	semistatic
Species	:	Oncorhynchus mykiss (Fish, fresh water)
Exposure period	:	48 hour(s)
Unit	:	mg/l
Limit test	:	
Analytical monitoring	:	no
Method	:	other: "Acute Toxicity Test"
Year	:	1972
GLP	:	no
Test substance	:	other TS: phthalic anhydride, purity is not specified
Method	:	Investigation was carried out in three stages. In stage I, lethal, toxic and permissible concentrations were determined. The permissible concentration is defined as the concentration in which a 100 % of the tests gave a positive result. That means, if survival of the fish for a period of 48 hours in a given concentration is observed. In stage II biotests with 9 several mixtures of the 28 compounds were carried out. In stage III a simulated pollutant (composed of all 28 compounds) was determined to find the dose established as permissible.
Remark	:	Accepted new scientific name for Salmo gairdneri: Oncorhynchus mykiss
Result	:	Permissible concentration, in which the compound was examined - individually: 5 mg/l (synthetical result) - in a group: 0.2 - 0.4 mg/l (composition of a simulated industrial wastewater) The mixture/group IX (which includes phthalic anhydride) had to be diluted with water in a relation of 1:1 - 1:1.22 so that the test might give a positive result. The dose of stage I had to be diminished >20 times than in stage III in order to be harmless again.
Test condition	:	- test organism: 2 years old animals, reared in the Fishery Experimental Station of the Agricultural College in Cracow, placed in aquaria for adaptation (10 - 12

days), during the test no feeding (for phthalic anhydride 6 fish were examined)
- test conditions:
renewal of solution once in 24 hour, average oxygenation 8.4 mg O2/l, temperature 16 - 21.5 °C (+/- 1 °C), well water was used, increase of pH during 24 hous from a value of 6.1 to 7.8

Reliability : (4) not assignable
Documentation insufficient for assessment

25.11.2004 (112)

Type : static
Species : Oryzias latipes (Fish, fresh water)
Exposure period : 48 hour(s)
Unit : mg/l
LC50 : > 1000
Limit test :
Analytical monitoring : no data
Method : other: "Acute Toxicity Test"
Year : 1986
GLP : no data
Test substance : other TS: Phthalic acid, purity is not specified

Source : Original literature in Japanese with English abstract
Test condition : The investigations were conducted at three temperatures: 10, 20 and 30°C.
Reliability : (4) not assignable
Original reference not translated

06.10.2005 (113)

Type : static
Species : other: tadpole of Bufo bufo japonicus SCHLEGEL (amphibian)
Exposure period : 24 hour(s)
Unit : mg/l
LC0 : >= 42
Limit test :
Analytical monitoring : no
Method : other: see test conditions below
Year : 1980
GLP : no data
Test substance : other TS: phthalic acid, no purity specified

Result : At all pH conditions no effect was observed above 42 mg/l with the exception of pH 5, where an effect occured at the highest concentration tested
Test condition : - Concentrations tested: 13, 18, 23, 32, 40, 42 mg/l
- Experiments were conducted at different pH conditions: 5, 6, 7, 8, 9, 10
- 1 to 4 weeks old tadpoles were used
- Test period: 24 h
- Test temperature: 25 °C
- Endpoint: mortality
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
21.10.2005 (114)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type : static
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)

Unit	:	mg/l
EC0	:	>= 640
EC50	:	> 640
Analytical monitoring	:	no
Method	:	other: Acute Toxicity Test
Year	:	1986
GLP	:	yes
Test substance	:	other TS: Phthalic acid, >99 % purity, received 2/19/82 from Fisher Scientific Company
Method	:	Method is following the procedures described in the MIC Environmental Assessment Method for Conducting Acute Toxicity Tests with Daphnia magna (Grueber and Adams, 1980) Environmental Sciences Report ES-80-M-6), and Methods for Acute Toxicity Tests with fish, macroinvertebrates and amphibians (U.S. EPA (1975) EPA 660/3-75-009).
Remark	:	The original pH of the 640 mg/l stock solution was 3.01 and afterwards raised with NaOH
Test condition	:	-test organisms: supplier was ESC Aquatic Laboratory, USA - age: less than 24 h - feeding in acclimation - dilution water (ranges during the test) was a mixture of distilled deionized water and well water from St. Peters, Missouri -test system: - temperature: 21.1 - 23.2 °C - alkalinity: 90 - 260 mg/l - hardness: 60 mg/l - pH: 7.9 - 8.8 - oxygen: 7.8 - 8.8 mg/l (Dissolved oxygen) - alkalinity, hardness and oxygen were measured at the beginning and at the end of the test - no dissolving agent was used - test concentrations (nominal): 40, 80, 160, 320, 640 mg/l - 10 daphnids x 3 replicates per concentration - no renewal of the test solution - exposure vessel: 250 ml beakers, containing 200 ml test solution (for each 10 daphnia) - no feeding during the test - no aeration during the test
Reliability	:	(2) valid with restrictions Comparable to guideline study with acceptable restrictions
Flag	:	Critical study for SIDS endpoint

21.07.2004 (115)

Type	:	static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	24 hour(s)
Unit	:	mg/l
EC50	:	140
Analytical monitoring	:	no
Method	:	ISO 6341 15 "Water quality - Determination of the inhibition of the mobility of Daphnia magna Straus (Cladocera, Crustacea)"
Year	:	2003
GLP	:	no data
Test substance	:	other TS: Phthalic acid, purity is not specified
Remark	:	Effect endpoint (E(L)C): immobilization and/or mortality. Range of test concentrations is not reported.
Result	:	The value of 140 mg/l represents the median between the concentration of 180 mg/l where all daphnia were immobile or died in 24h and the concentration of 100 mg/l where all daphnia survieved.

Test condition	:	- test organism: Daphnia magna, age: max. 24 h - testing was performed in a chemically and physically defined standardized aqueous medium according to ISO Standard. Quality of the culture medium: CaCl2 294 mg/l, MgSO4x7H2O 123.3 mg/l, NaHCO3 64.8 mg/l, KCl 5.8 mg/l, saturated with oxygen - pH was adjusted to 7.8 +/- 0.2 - temperature 20°C - four controls with test solution and four controls with pure medium, 5 daphnids/chamber (5 organisms/20 ml) - pH value and oxygen content were measured before and after the test - the test was carried out in the dark
Reliability	:	(2) valid with restrictions Study meets generally accepted scientific principles
Flag	:	Critical study for SIDS endpoint
21.07.2004		(116)

Type	:	static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	24 hour(s)
Unit	:	mg/l
EC50	:	4900
Analytical monitoring	:	no data
Method	:	other: see test conditions
Year	:	1996
GLP	:	no data
Test substance	:	other TS: o-Phthalic acid, purity is not specified
Remark	:	These toxicity data or methods, respectively, have been reported previously (see references).
Result	:	The IC50-values (mol/l) at 24 h were calculated from the dose-response relationships using the least-squares regression analysis. The corresponding IC50-values at different pH: pH 6.0: 4370 mg/l pH 7.8: 4900 mg/l pH 9.0: 6460 mg/l
Test condition	:	- Daphnids were cultured parthenogenetically in an environmental chamber at 22 +/- 1 °C - Photoperiod 14 hours, 10 hours dark - For culturing a green algae diet was fed - 6 to 24 hours old daphnids were used for toxicity test, 10 daphnids in 25 ml of test water - Incubation 24 hours at 22 +/- 1 °C - test solutions always regulated at pH 6.0, 7.8, and 9.0, each +/- 0.1, determination at the beginning and end of each test - 5 replicates for every concentration - Results were considered valid, when oxygen concentration was > 60 % of saturation, and if immobilization in controls was zero at the end of experiment - Endpoint: immobilization concentration (IC)
Reliability	:	(2) valid with restrictions Basic data given
Flag	:	Critical study for SIDS endpoint
25.11.2004		(107) (108)

Type	:	
Species	:	other aquatic crustacea: Thamnocephalus platyurus
Exposure period	:	24 hour(s)
Unit	:	mg/l
EC50	:	220
Analytical monitoring	:	no

Method	:	other:
Year	:	2003
GLP	:	no data
Test substance	:	other TS: Phthalic acid, purity is not specified
Method	:	The definitive and the range finding test were performed in accordance with the standard operation procedure described in Thamnotokit Ftm protokol (Creasel Ltd., Deinze, Belgium).
Remark	:	Effect endpoint (E(L)C): immobilization and/or mortality. Range of test concentrations is not reported.
Test condition	:	- test organism: instar larva of the Thamnocephalus platyurus, hatched from the cysts - preliminary test to ascertain the appropriate concentration range by decimal dilution - testing was performed in a defined standardized aqueous medium according to ISO Standard. Quality of the culture medium: CaSO4x2H2O 30 mg/l, NaHCO3 48 mg/l, MgSO4x7H2O 30 mg/l, KCl 2 mg/l, saturated with oxygen, pH was adjusted to 7.4 +/- 0.2 - 30 organisms for each dilution and control - pH value and oxygen content were measured before and after the test - the test was carried out in the dark
Reliability	:	(2) valid with restrictions Study meets generally accepted scientific principles
Flag	:	Critical study for SIDS endpoint
25.11.2004		(116)

Type	:	static
Species	:	other: Chironomus plumosus (aquatic)
Exposure period	:	48 hour(s)
Unit	:	mg/l
EC50	:	> 72
Analytical monitoring	:	no
Method	:	other: Static acute toxicity test
Year	:	1980
GLP	:	no data
Test substance	:	other TS: Phthalic acid, no purity specified
Method	:	Standard methods for static toxicity test (Committee on methods of toxicity tests with aquatic organisms 1975) Techniques to rear laboratory populations of the midges, see for further details Biever KD (1965). A rearing technique for the colonization of chironomid midges. Ann. Entomol. Soc. Am. 58, 135-136).
Test condition	:	- static test system - late third and early fourth-instar midge larvae - Well water ph 7.4, total hardness 270 mg/l CaCO3 - Temperature 22 +/- 1 °C - 16 hours light, 8 hours dark photoperiod - Solvent ethanol (concentration < 0.1 ml/l) - Endpoint: Immobilisation
Reliability	:	(2) valid with restrictions Basic data given
Flag	:	Critical study for SIDS endpoint
25.11.2004		(117) (118)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	other algae: Desmodesmus subspicatus
Endpoint	:	growth rate
Exposure period	:	72 hour(s)

Unit : mg/l
EC0 : >= 100
Limit test : yes
Analytical monitoring : yes
Method : OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year : 2004
GLP : yes
Test substance : other TS: phthalic acid, purity: 99.5 %

Result : With pH adjustment, the recovery rate was > 98 %, therefore the nominal value was reported. The result is related to both endpoints growth rate and biomass.
Without pH adjustment at 100 mg/l 100 % inhibition was observed after 72 hours; pH was determined to be in the range of 4.9 to 5.1.

Test condition : - Flasks (300 ml) with cotton plug were filled with 100 ml testmedium and algae
- Test system was continuously illuminated
- Growth of the unicellular green algae was checked daily over a period of 3 days
- Initial cell density: 10000 cells/ml
- Tested concentration: 100 mg/l with and without neutralization
- The stability of the test substance was experimentally determined with HPLC before and after an exposure of 72 hours

Test substance : CAS-No.: 88-99-3, Lot No.: A0163727
Reliability : (1) valid without restriction
GLP guideline study
Flag : Critical study for SIDS endpoint
20.10.2005 (119)

Species : Selenastrum capricornutum (Algae)
Endpoint : biomass
Exposure period : 96 hour(s)
Unit : mg/l
EC50 : 4.14
Limit test : no
Analytical monitoring : yes
Method : other: Standard procedure from the Federal Register Vol.50, No.188, Part 797, Sec.797.1050 Algal Acute Toxicity Test
Year : 1989
GLP : no data
Test substance : other TS: phthalic anhydride, purity is not specified

Result : Test concentrations and results related to nominal concentrations.
Resluts of analytical monitoring:
Recovery for each concentration (avg., mg/l):

Conc. before testing		after testing
20	20.7	0.0
10	0.2	7.1
5	0.2	4.1
2.5	2.4	1.9
1.25	1.1	0.3
0.625	0.7	0.8
0.3125	0.3	0.4

Recovery rates (% from avg. conc.):

Conc. before testing		after testing
20	104	0
10	2	71
5	2	82
2.5	96	76

		1.25 88 24 0.625 112 128 0.3125 96 128
Test condition	:	- Range finding test was previously conducted at test concentrations of 0.01, 0.1, 1, 10, 100 and 1000 mg/l whereby the highest test concentrations were pH adjusted - The definitive test was conducted at 7 test concentrations : 0.3125, 0.625, 1.25, 2.5, 5, 10 and 20 mg/l (nominal) without pH adjustment; 3 replicates; static test - pH was only measured at the beginning and at the end of the test at the lowest and highest test concentrations. - Initial pH: 5.5 (high conc.) and 8.5 (low conc.) - Final pH: 5.7 (high conc.) and 7.5 (low conc.) - Oxygen-concentration was not monitored - The concentrations were analytically determined with HPLC before and after testing - Temperature: 24 °C +/- 2°C - Continuous light - The EC50 was calculated by ANOVA using the experimental data
Reliability	:	(3) invalid Significant methodological deficiences. Main test conducted without pH adjustment

23.09.2004 (120)

Species	:	other algae: Scenedesmus subspicatus CHODAT
Endpoint	:	growth rate
Exposure period	:	7 day(s)
Unit	:	mg/l
EC50	:	258
Limit test	:	
Analytical monitoring	:	no
Method	:	other: modified to ISO 8692
Year	:	2003
GLP	:	no data
Test substance	:	other TS: Phthalic acid, purity is not specified
Remark	:	Accepted new scientific name for Scenedesmus subspicatus: Desmodesmus subspicatus. It is not clear whether the algae are within the exponential growth throughout the whole exposure period of 7 days. The counting of samples after incubation of seven days showed that the algae at the end of incubation were not in logarithmic or exponential phase of growth. The cells were not counted during the time interval of seven days, so the author can not conclude after which day the culture in the different samples end with its reproduction
Result	:	Endpoint biomass: 7 d EC50: 506 mg/l
Test condition	:	- Cultures of S. subspicatus were obtained from the National Institute of Biology, Ljubljana, Slovenia - 7 day incubation period with a 12 hour day/night rhythm of lighting at 100 µE/m2/s - Static conditions - Each sample contained approx. 10000 cells/ml algal culture that grew in the control samples to 5.2 - 6.8 x 10E6 cells/ml - Concentrations in a range of 84 - 840 mg/l were chosen so that 4 - 5 of them covered 10 - 90 % inhibition - for each concentration 4 replicate samples and reagent blank samples were prepared - pH was adjusted to 8.3 +/- 0.2 - algal cells were counted at the beginning of the experiment (day 0) and after 7 days incubation

Reliability	:	(3) invalid It is not clear whether the algae were within the exponential growth throughout the whole exposure period of 7 days

06.10.2005 (121) (116)

Species	:	other algae: Scenedesmus sp. and Microcystis sp.
Endpoint	:	other: growth inhibition
Exposure period	:	
Unit	:	
Limit test	:	
Analytical monitoring	:	yes
Method	:	other: Growth inhibition test
Year	:	2002
GLP	:	no data
Test substance	:	other TS: phthalic acid
Method	:	Growth inhibition of freshwater algae by decomposed material of plants was determined and the inhibitory chemicals were identified using GC/MSD.
Result	:	The inhibitory effect on the growth of Scenedesmus sp. of rotted materials (on average): 2-days: 57% 8-days: 49% 14-days: 41% 21-days: 42% For Microcystis sp., an antialgal effect of the 2-day rotted materials of 93% (on average) is reported. The antialgal effect decreased relative to the rotting time flow for both algae. One of the inhibitory chemicals, released from the rotted plants, was identified as 1,2-benzenedicarboxylic acid (o-phthalic acid).
Test condition	:	- Test material: Korean pine needles, Korean pine chips, pine needles, pine chips, barley straw, rice straw, mugwort and chrysanthemum - Test solution: 1 g of each material was placed in a 250 ml conical flask, 200 ml of natural water was added, and the flasks were maintained at 20 ° C for 2, 8, 14, and 21 days, after incubation the samples were filtered with 5 A filter paper - Seedling: the filtrate was added to the both two fresh algal mediums in 250 ml flasks, containing about 10E+4 cells/ml in each case - Endpoint: The inhibition of growth was obtained by quantifying the chlorophyll a content after 5 days of incubation. Culture medium for algae was prepared for Scenedesmus sp. according to DIN 38412 Part33; for Microcystis sp. according to Ichimura and Ito (1977)
Reliability	:	(3) invalid Unsuitable test system

06.10.2005 (122)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

Type	:	aquatic
Species	:	activated sludge
Exposure period	:	3 hour(s)
Unit	:	mg/l
EC50	:	> 1000
Analytical monitoring	:	no
Method	:	ISO 8192 "Test for inhibition of oxygen consumption by activated sludge"
Year	:	1984
GLP	:	no data
Test substance	:	other TS: phthalic anhydride, purity >= 99.8 %

Method	:	ETAD recommended method no. 103 (corresponds for the most part to the test methods OECD 209)
Test condition	:	- test concentration of activated sludge: 0.38 g/l ss (=suspended solids) - incubation time with permanent aeration - pH of test concentrations: 7.3 - 7.4
Reliability	:	(2) valid with restrictions Basic data given
Flag	:	Critical study for SIDS endpoint

25.11.2004 (123)

Type	:	aquatic
Species	:	Pseudomonas putida (Bacteria)
Exposure period	:	16 hour(s)
Unit	:	mg/l
EC50	:	213
Analytical monitoring	:	no
Method	:	other: ISO 10712, 1995 Pseudomonas putida growth inhibition test (Pseudomanas cell multiplication inhibitiontest)
Year	:	2003
GLP	:	no data
Test substance	:	other TS: phthalic acid, purity is not specified
Method	:	The percentage of cell multiplication inhibition was calculated in conformity with the ISO standard (ISO, 1995).
Remark	:	The inhibition effect was determined by the increase of turbidity of bacterial cultures at chosen logarithmic dilutions of the initial concentration of the test substance
Test condition	:	- incubation time 16 +/- 1 hours at 26 °C - testing was performed in defined mineral medium, composed for the test as follows: NaNO3 500 mg/l, K2HPO4 60 mg/l, D8+)Glucose monohydrate 2000 mg/l, MgSO4 x 7 H20 200 mg/l, Iron(III) citrate 0.5 mg/l, pH was adjusted to 7.4 +/- 0.3 - measurement of turbidity
Reliability	:	(2) valid with restrictions Basic data given
Flag	:	Critical study for SIDS endpoint

25.11.2004 (116)

Type	:	
Species	:	other bacteria: Azospirillum brasilense (DSM 2297)
Exposure period	:	48 hour(s)
Unit	:	g/l
LOEC	:	1
Analytical monitoring	:	no
Method	:	other: Bacterial Assay (Swarming Inhibition Test)
Year	:	1987
GLP	:	no data
Test substance	:	other TS: phthalic anhydride, purity is not specified, purchased by FLUKA GmbH (Neu-Ulm , Germany)
Remark	:	Not relevant for environmental assessment
Test condition	:	- Bacteria cultured at 30 °C in a liquid NB-Medium up to an optical density of 0.6 (400 - 600 nm). This suspension was directly used for the assay. - Media: NB medium (pH 7.0); Nutrient broth 10 g; Yeast extract 5 g; NaCl 5 g; Agar 12 g; distilled water 1000 ml - Petri dishes (90 mm diameter) containing 20 ml of this medium - Test substance diluted with DMSO (1:1) - 10 µl of each concentration of test substance plus 10 µl cell suspension of

bacteria were mixed
- four times 5 µl of this mixture were placed on the agar surface, thus the petri dish was inoculated with for spots of 5 µl
- after 48 h of incubation at 25 °C, the circular spreading zone swere measured and compared to the zones without toxin

Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

21.07.2004 (124) (125)

Type :
Species : other bacteria: Proteus mirabilis (ATCC 27035)
Exposure period : 24 hour(s)
Unit : g/l
LOEC : 5
Analytical monitoring : no
Method : other: Bacterial Assay (Swarming Inhibition Test)
Year : 1987
GLP : no
Test substance : other TS: phthalic anhydride, purity is not specified, purchased by FLUKA GmbH (Neu-Ulm , Germany)

Test condition : - Bacteria cultured at 30 °C in a liquid NB-Medium up to an optical density of 0.6 (400 - 600 nm). This suspension was directly used for the assay.
- Media:
NB medium (pH 7.0); Nutrient broth 10 g; Yeast extract 5 g; NaCl 5 g; Agar 12 g; distilled water 1000 ml
- Petri dishes (90 mm diameter) containing 20 ml of this medium
- Test substance diluted with DMSO (1:1)
- 10 µl of each concentration of test substance plus 10 µl cell suspension of bacteria were mixed
- four times 5 µl of this mixture were placed on the agar surface, thus the petri dish was inoculated with for spots of 5 µl
- after 24 h of incubation at 25 °C, the circular spreading zone swere measured and compared to the zones without toxin

Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

15.07.2004 (124) (125)

Type :
Species : other bacteria: Bacillus thuringiensis (ATCC 10792)
Exposure period : 24 hour(s)
Unit : g/l
LOEC : 5
Analytical monitoring : no
Method : other: Cup Plate Assay (Growth Inhibition)
Year : 1987
GLP : no
Test substance : other TS: phthalic anhydride, purity is not specified, purchased by FLUKA GmbH (Neu-Ulm , Germany)

Method : According to the Method of Lenz P, Suessmuth R, and Seibel E (1986). Development of sensitive bacterial tests, exemplified by two mycotoxins. Toxicology 40, 199-205.

Test condition : - Bacteria were cultured in liquid NB medium up to a cell density of ca. 1.0 optical density (OD 400 - 600 nm), then the OD was adjusted to 0.05 (400 - 600 nm). NB/2 agar plates were inoculated with 50 µl of this suspension (10 E+5 cells per plate)
- Media:

NB/2 medium (pH 7.0); Nutrient broth 5 g; Yeast extract 2.5 g; NaCl 2.5 g; Agar 12 g; distilled water 1000 ml
- Petri dishes (90 mm diameter) containing 10 ml of this medium
- the cup plate diffusion assay was carried out as a hole-test with inoculated agar plates
- a number of holes were punched into the agar and filled with the test substance solution
- Test substance diluted with DMSO (1:1)
- Incubation time 4 h at 4 °C and 20 h at 25 °C

Reliability : (2) valid with restrictions
Test procedure in accordance with national standard methods with acceptable restrictions

15.07.2004 (124) (125)

Type : aquatic
Species : Vibrio fisheri (Bacteria)
Exposure period : 15 minute(s)
Unit : mg/l
EC50 : 6.61
Analytical monitoring : no data
Method : other: see test conditions
Year : 1998
GLP : no data
Test substance : other TS: o-phthalic acid, purity is not specified

Result : Ecotoxicological descriptors were the concentration values causing a 50 % inhibition of bioluminescence after 15 min exposure.
Test condition : - bacteria originated from the Institute of Soil Science, Academia Sinica, Nanjing, China
- temperature: 20 +/- 2 °C
- bioluminescence measured after 15 and 30 minutes by means of Toxicity Analyzer DXY-2
- pH 5.7

Reliability : (3) invalid
Unsuitable test system

23.07.2004 (107) (108)

4.5.1 CHRONIC TOXICITY TO FISH

Species : Salmo gairdneri (Fish, estuary, fresh water)
Endpoint : other: Mortality, Total Embryotoxicity
Exposure period : 60 day(s)
Unit : mg/l
NOEC : 10
LOEC : 32
Analytical monitoring : no data
Method : other: according to OECD Guideline Draft "Early Life Stage"
Year : 1990
GLP : no data
Test substance : other TS: phthalic anhydride, purity >= 98 % (FA Merck)

Method : Van Leeuwen CJ, Espeldoorn A, and Mol F (1986). Aquatic toxicological aspects of dithiocarbamates and related compounds. III. Embryolarval studies with Rainbow trout (Salmo gairdneri). Aquat Toxicol 9: 129-145.
Remark : Accepted new scientific name for Salmo gairdneri: Oncorhynchus mykiss
Result : EC50 (Total Embryotoxicity): 44.1 mg/l
LC50 : 44.2 mg/l
LOEC (mortality): 32 mg/l
LOEC (total embryotoxicity): 32 mg/l

LOEC (length): 32 mg/l
LOEC (weight): 32 mg/l

LOEC: The lowest concentration which differed significantly from the control.

Geometric series of 7 test concentrations using a factor of 3.2 was used. With a factor of 3.2 the next lowest concentration is 10 mg/l which corresponds to the no effect concentration (NOEC) of 10 mg/l.

The LC50 and 95 % confidence limits were determined according to Kooyman (1981)*. Concentrations affecting survival with more than 50 % were excluded from the statistical analyses. The Bartlett test was used to test the data for homogeneity of variances. Differences were considered significant at alpha < 0.01.

* Kooyman SALM (1981). Parametric analyses of mortality rates in bioassays. Water Res. 15, 107-119.

Test condition : - test organism:
Salmo gairdneri; freshly, artificially spawned eggs from, obtained from a fish hatchery (Vaassen, Gelderland); 3 h after fertilization, egg samples (size 100); no feeding throughout the test
- test vessel:
15-l glass tank, 10 l volume
- test medium:
reconstituted water, hardness 50 mg/l (CaCO3), pH 7.7 +/- 0.2, temperature 10 +/- 1 °C, oxgen concentration 10.8 +/- 0.2, prepared according Alabaster and Abraham (1965)*, renewed three times a week (stock solution prepared fresh at each renewal), continuously aerated
- solvent:
DMSO < 100 µl/l
- test concentration:
5 - 7, a solvent and blank control; range between the concentrations was 3.2
- replicates:
test conducted in duplicate
- room temperature:
10 +/- 1 °C
- lighting:
during embryogenesis darkness; after hatching a photoperiod of 12 h light/12 h dark
- test period:
60 days
- controls:
regularly inspection for dead specimens and unfertilized eggs which were removed; pH measurements at regular intervals; no verification of the test compound during the experiment; determination of wet weight and length performed only at the end of the test

* Alabaster JS and Abram FSH (1965). Estimating the toxicity of pesticides to fish. Pest. Articles News Summaries 11, 91-97.

Reliability : (2) valid with restrictions
Basic data given

Flag : Critical study for SIDS endpoint

25.11.2004 (106)

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

Species	:	other terrestrial plant: Lactuca sativa L. cv. Great Lakes
Endpoint	:	other: inhibition of fruit germination
Exposure period	:	3 day(s)
Unit	:	mg/l
EC50	:	731
Method	:	other: Inhibition of fruit germination
Year	:	1975
GLP	:	no data
Test substance	:	other TS: phthalic acid, purity is not specified
Method	:	Test method described in: Reynolds T (1975). Characterization of osmotic restraints on lettuce fruit germination. Ann. Bot. 39, 791 - 796.
Result	:	Result given as: EC50 = 4.4 +/- 0.6 mmol/l, which corresponds to 731 +/- 100 mg/l. (Molecular weight of phthalic acid, 166.13 g/mol)
Test condition	:	- Samples were grown on 0.5 % agar media in 10 ml-plastic containers sealed with snap-on lids at a temperature of 30 °C - 20 lettuce fruits per concentration were tested - 5 replicates
Test substance	:	The test compounds tested were received from the manufactures Aldrich Chemical Co. Ltd., Sigma Chemical Co. Ltd., and Fluka Chemicals Ltd. The manufacture for phthalic acid is not further specified
Reliability	:	(2) valid with restrictions Study well documented, meets generally accepted scientific principles.
Flag	:	Critical study for SIDS endpoint
11.08.2004		(43) (126)

Species	:	other terrestrial plant: Gossypium hirsutum L.
Endpoint	:	other: relative root growth
Exposure period	:	
Unit	:	
Method	:	
Year	:	1986
GLP	:	no data
Test substance	:	other TS: phthalic acid, purity is not specified
Method	:	Short-term, splitroot experiments with cotton (Gossypium hirsutum L.) taproots as the growth indicator were conducted to determine if the presence of phthalic acid in soil solutions affect Al-phytotoxicity. The relative length of cotton taproots, 48 h after growing, into various concentrations of phthalic acid was measured.
Result	:	Phthalic acid showed essentially no root-protection capacity at acid levels up to 50 µmol/L.
Reliability	:	(4) not assignable Documentation insufficient for assessment
22.07.2004		(127)

Species	:	other terrestrial plant: Lycopersicon esculentum Mill, cv TVR-2
Endpoint	:	other: root length
Exposure period	:	
Unit	:	
Method	:	
Year	:	1993
GLP	:	no data
Test substance	:	other TS: phthalic acid, purity is not specified
Method	:	The substances were identified by GC/MS.
Remark	:	The study was undertaken to separate phytotoxic substances from residual nutrient solution (RNS) and the residual activated charcoal (RAC), collected after hydroponic culture of tomato.
Result	:	Beside other organic acids the phthalic acid was identified as one of the phytotoxic acids.
Test condition	:	The concentrate of RNS was fractionated into 5 organic fractions in order to separate the phytotoxic substances. The pH of the aqueous phase was adjusted at first to 2 and then to 8 (pH 2-8 system), and in another experiment, at first to 8 and then to 2 (pH 8-2 system). The phytotoxicity of the different concentrates were presented by the ration of the root length of tomato in the test solution to that in the control solution.
Reliability	:	(4) not assignable Documentation insufficient for assessment

22.07.2004 (128)

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

Species	:	other: White leghorn
Endpoint	:	other: embryotoxicity
Exposure period	:	11 day(s)
Unit	:	other: mg/egg
ED 50	:	.05631
Method	:	other:
Year	:	1990
GLP	:	no data
Test substance	:	other TS: phthalic anhydride, purity is not specified
Result	:	The corresponding ED50 is 0.056313 mg/egg. Slope of the dose- response curve was 1.6 (tan alpha). The maximum percentage of malformed embryos was 20. The result (11d-ED 50) is given in 0.38 µmol per egg.
Test condition	:	- solvent: acetone (analytical grade) or water; 10 eggs of each batch were injected with 5 µl of acetone as solvent control - solvent control: altogether 600 embryos were tested and the total number of affected embryos was 3.2 % - test organism: 3-day chicken embryos - exposure: injection of test solution on the visible embryo into the air chamber of the egg - incubation time: 14 days; three days after injection the embyroys were scored and

discarded and the remaining ones checked for deaths and malformations, 11 days after treatment

Reliability : (4) not assignable
Secondary literature

25.11.2004 (129) (106)

Species : other: tadpoles of Bufo bufo japonicus SCHLEGEL (amphibian)
Endpoint :
Exposure period :
Unit :

Remark : Results of Nishiuchi (1980) see IUCLID Chapter 4.1
21.10.2005

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

23.07.2004

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In Vitro/in vivo : In vivo
Type :
Species : mouse
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :
Route of administration : i.p.
Exposure time : 3 day(s)
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st:
2nd:
3rd:
Toxic behaviour :
Deg. product :
Method :
Year : 1978
GLP : no
Test substance : other TS: [14-C] phthalic anhydride, purity not specified

Method : CD-1 mice received [14-C] phthalic anhydride at 80 mg/kg bw/day on days 11, 12, and 13 of gestation. Six hours after the last dose, the animals were sacrificed and the tissues collected. The radioactivity, total and bound, was measured by scintillation counting technique.
Result : Bound radioactivity was found in all tissues examined.
Reliability : (4) not assignable
Documentation insufficient, abstract only

04.05.2006 (130)

In Vitro/in vivo : In vivo
Type :
Species : rabbit
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :
Route of administration : i.p.
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st:
2nd:
3rd:
Toxic behaviour :
Deg. product :

Method : other: Administration of [14-C]- or [3H]-phthalic anhydride to pregnant rabbits during embryogenesis.
Year : 1978
GLP : no
Test substance : other TS: [14-C]- or [3H]-phthalic anhydride, purity not specified

Result : Bound radioactivity was found in all tissues examined
Reliability : (4) not assignable
Documentation insufficient, abstract only
01.03.2006 (130)

In Vitro/in vivo : In vitro
Type :
Species : other: in vitro
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :
Method :
Year : 1978
GLP : no
Test substance : other TS: [14-C]-phthalic anhydride, purity not specified

Remark : In vitro, very small quantities of [14C]-phthalic anhydride were found to bind covalently to bovine serum albumin (BSA) after one hour incubation at 37 degree Celsius
Reliability : (4) not assignable
Documentation insufficient, abstracts only
01.03.2006 (131)

In Vitro/in vivo : In vivo
Type :
Species : mouse
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :
Route of administration : i.p.
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st:
2nd:
3rd:
Toxic behaviour :
Deg. product :
Method :
Year : 1978
GLP : no
Test substance : other TS: [14-C]-phthalic anhydride, purity not specified

Remark : Bound radioactivity was found in the foetuses of mice receiving [14C]-phthalic anhydride by the intraperitoneal route, indicating the phthalic

anhydride or a metabolite of the substrate may can cross the placenta.

Reliability : (4) not assignable
Documentation insufficient, abstract only

01.03.2006 (131)

In Vitro/in vivo : In vitro
Type :
Species :
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :
Method :
Year : 1986
GLP : no
Test substance : other TS: purity not specified

Remark : Phthalic anhydride has been shown to bind to human serum albumin (HSA). 30 mg phthalic acid was dissolved in 1 ml of acetone and added to 10 ml of 2% HSA in 9% sodium bicarbonate at 4°C and incubated for 1 hour. No further data available.
Reliability : (4) not assignable
Poor documentation

28.04.2006 (132)

In Vitro/in vivo : In vivo
Type :
Species :
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :
Method :
Year : 1977
GLP : no
Test substance : other TS: occupational exposure purity not specified

Method : The excretion of phthalic anhydride in humans has been investigated in a study where urine samples were collected from nine subjects occupationally exposed to phthalic anhydride, primarily by the inhalation route. Samples were taken pre-shift (7:00 hours) on-shift, post-shift (15:00 hours) and in the evening and the next morning after work day. Airborne phthalic anhydride levels ranged from 0.03 to 10.5 mg/m3 (mean value, MMAD not stated), determined from personal air samples from the worker breathing zone. Urine was also taken from a control group of 22 persons not occupational exposed to phthalic anhydride. Phthalic anhydride is converted to phthalic acid in the presence of water. Phthalic acid concentration in the urine was measured after esterification with methanol by electron capture gas chromatography, and expressed in terms of urinary creatinine.

Urine samples were also subjected to acid, alkaline, and enzymatic hydrolysis by beta-glucuronidase or aryl sulphatase.
Result : At low atmospheric phthalic anhydride concentrations (mean +/- SD; 0.15

+/- 0.15 mg/m3, range 0.03 - 0.33 mg/m3, n=5) the excretion of phthalic acid increased from the pre-shift (7:00 hours) concentration to the post-shift (15:00 hours) concentration and decreased then until the pre-shift concentration was again reached. The pre-shift phthalic acid concentration in the urine (0.49 +/- 0.15 µmol/mmol creatinine) were not significantly different from those of occupationally unexposed people (0.34 +/- 0.25 µmol/mmol creatinine, range 0.02-0.089 µmol/mmol creatinine, n=22). Exposure to higher concentrations of phthalic anhydride in air (1.63 +/- 0.13 mg/m3, n=2) resulted in a body load of phthalic acid which was not totally cleared overnight, and with pre-shift phthalic acid concentrations in the urine with a mean value three times the mean control value (1.02 +/- 0.25 µmol/mmol creatinine). One worker exposed to high concentration of phthalic anhydride (10.2 mg/m3) had a pre-shift urinary concentration of 4.8 µmol of phthalic acid /mmol creatinine; approximately 14 times that of the control group. The concentration of phthalic acid in the urine was found to increase from the pre-shift level to a maximum in the immediate post-shift or evening urine sample.

The concentration then decreased, with a half-life of approx. 14 hours (no further information on half-life estimation)

No evidence was seen of conjugate formation.

Thus, workers occupationally exposed to atmospheric phthalic anhydride absorbed the substance with some being excreted in the urine as unconjugated phthalic acid.

Reliability : (4) not assignable
Limited documentation, no further information on half-life estimation
Flag : Critical study for SIDS endpoint
06.03.2006 (133)

In Vitro/in vivo : In vivo
Type :
Species :
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :
Method :
Year : 1977
GLP : no
Test substance : other TS: occupational exposure purity not specified

Method : Urine samples were obtained from 48 workers in jobs with high exposure to phthalates and from 47 workers in jobs with low exposure. The airborne concentration of di-ethylhexyl)phthalate (DEHP) ranged from 20 to 4110 µg/m3 and the concentration of phthalic anhydride (PA) ranged from 4 to 203 µg/m3.
Result : The most heavy exposed workers had the highest mean postshift urine phthalate concentration (7.6 nmol/ml urine), and also the greatest mean increase (4.4 nmol/ml) in preshift to postshift urine phthalate level. Twofold increases over the shift in urine phthalate concentration and postshift phthalate level greater than 10 mmol/ml were observed in 8 (25%) of 32 chemical operators, but non of the control workers without exposure.
Reliability : (3) invalid
Mixed exposure to DEHP and phthalic anhydride with higher DEHP level

than phthalic anhydride level
17.03.2004 (83)

Method :
Year : 2001
GLP : no
Test substance : other TS: phthalic anhydride, purity not specified

Method : Phthalic anhydride hydrolyzes rapidly in the presence of water forming phthalic acid. Half-life for phthalic anhydride was 30.5 seconds at pH 7.24. At pH 6.8 the half-life of phthtalic anhydride in water was prolonged to 61 seconds.
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
06.03.2006 (134)

5.1.1 ACUTE ORAL TOXICITY

Type : LD50
Value : = 1530 mg/kg bw
Species : rat
Strain : other: Wistar-II
Sex : male
Number of animals : 10
Vehicle : other: DMSO
Doses : 100, 500, 1000, 2000, 3100, 5000 mg/kg bw in DMSO
Method : other: 10 male rats/dose (bw: 160-180g), single oral application by gavage dissolved in DMSO (2 ml/100 g bw), observation time: 14 d, calculation of LD50 according to Fink (1965) Arzneim.-Forsch. 15, 624
Year : 1978
GLP : no
Test substance : other TS: approx. 99.8 % purity

Result : Dose-group, time of death, No of rats that died, No of rats with symptoms:
100 mg/kg bw, no deaths, 0/10, 0/10
500 mg/kg bw, 3-4 d, 2/10, 10/10
1000 mg/kg bw, 3 d, 2/10, 10/10
2000 mg/kg bw, 2-3 d, 4/10, 10/10
3100 mg/kg bw, 2-3 d, 9/10, 10/10
5000 mg/kg bw, 2 d, 10/10, 10/10
symptoms: sedation, imbalance, and bloody eyes
no gross or histopathological examination
Reliability : (2) valid with restrictions
Gross or histopathological examination was not performed, big volumes of DMSO was used as a solvent
Flag : Critical study for SIDS endpoint
03.03.2004 (135)

Type : LD50
Value : = 4020 mg/kg bw
Species : rat
Strain : other: albino, no further data
Sex : male
Number of animals : 5
Vehicle : other: corn oil
Doses : 2150, 3160, 4640, 6810 mg/kg bw as 25 % suspension in corn oil

Method	:	other: single oral application by gavage, dosing volume not mentioned, observation period up to 14 days. Parameters investigated: time of death, time of recovery, record of symptoms, gross autopsy (organs not specified).
Year	:	1970
GLP	:	no
Test substance	:	other TS: no data on purity, melting point:130.8°C
Result	:	all rats: signs of intoxication up to 4 hours after application of phthalic anhydride: hypothermia, lethargy, ruffed fur, diuresis, diarrhea. 2150 mg/kg bw: no death, recovery within the first day after dosing. 3160 mg/kg bw: 1/5 rat died within 12-24 hrs, 4/5 recovered within 2 days. 4640 mg/kg bw: 4/5 rats died within 2 days after dosing, 1/5 rat recovered within 3 days after dosing. 6810 mg/kg bw: 2/5 rats died within the first 4 hrs. Further 2 rats died within 3 days. One animal recovered after 4 days. Gross autopsy: survivors: no significant findings; decedents: inflammation of gastrointestinal tract, hyperaemia of liver and lungs.
Reliability	:	(4) not assignable Industrial Biotest Laboratories (IBT) unreliable test institute
26.11.2004		(136)

Type	:	LD50
Value	:	ca. 2500 - 5000 mg/kg bw
Species	:	rat
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	no data
Doses	:	no data
Method	:	other: no further information available
Year	:	1964
GLP	:	no
Test substance	:	other TS: no data on purity
Remark	:	Animals died from tubular necrosis of the kidneys.
Reliability	:	(4) not assignable Insufficient documentation: no experimental details given
17.03.2004		(137)

Type	:	LD50
Value	:	ca. 4500 mg/kg bw
Species	:	rat
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	other: suspension in traganth
Doses	:	no data
Method	:	other: observation period: 8 days. No further data available
Year	:	1955
GLP	:	no
Test substance	:	other TS: no data on purity
Reliability	:	(4) not assignable Documentation insufficient for assessment
22.03.2004		(8) (138)

Type	:	LD50
Value	:	ca. 800 - 1600 mg/kg bw
Species	:	rat
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	no data
Doses	:	no data
Method	:	other: no further information available
Year	:	1962
GLP	:	no
Test substance	:	other TS: no data on purity
Reliability	:	(4) not assignable Secondary literature

17.03.2004 (139) (140)

Type	:	LD50
Value	:	ca. 5800 mg/kg bw
Species	:	rat
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	other: solution in water pH 7.5
Doses	:	no data
Method	:	other: Observation period: 8 days. No further data available
Year	:	1955
GLP	:	no
Test substance	:	other TS: no data on purity
Reliability	:	(4) not assignable Documentation insufficient for assessment

22.03.2004 (8)

Type	:	LD50
Value	:	= 2500 - 5000 mg/kg bw
Species	:	rat
Strain	:	other: no data
Sex	:	no data
Number of animals	:	2
Vehicle	:	no data
Doses	:	1000, 2500, 5000, 10000 mg/kg bw
Method	:	other: no data
Year	:	1954
GLP	:	no
Test substance	:	other TS: no data purity
Result	:	Animals dosed with 1000 mg/kg bw had no symptoms. Animals dosed with 2500 mg/kg bw showed hyperventilation and died. Animals dosed with 5000 and 10000 mg/kg bw died. No further data
Reliability	:	(4) not assignable Documentation insufficient for assessment

17.03.2004 (141)

Type	:	LDLo
Value	:	= 680 mg/kg bw
Species	:	rat
Strain	:	no data
Sex	:	no data

Number of animals :
Vehicle : no data
Doses : no data
Method : other: no further information available
Year : 1969
GLP : no
Test substance : other TS: no data on purity

Reliability : (4) not assignable
Insufficient for assessment
05.02.2004 (142)

Type : other: LD40
Value : 200 - 1500 mg/kg bw
Species : rat
Strain : no data
Sex : no data
Number of animals :
Vehicle : no data
Doses : no data
Method : other: no further information available
Year : 1982
GLP : no data
Test substance : other TS: no data on purity

Reliability : (4) not assignable
05.02.2004 (143)

Type : LD50
Value : = 1500 mg/kg bw
Species : mouse
Strain : no data
Sex : no data
Number of animals :
Vehicle : no data
Doses : no data
Method : other: no further information available
Year : 1982
GLP : no data
Test substance : other TS: no data on purity

Reliability : (4) not assignable
Documentation insufficient for assessment
05.02.2004 (143)

Type : LD50
Value : = 2210 mg/kg bw
Species : mouse
Strain : other: white mice
Sex : no data
Number of animals :
Vehicle : no data
Doses : no data
Method : other: no further information available
Year : 1969
GLP : no
Test substance : other TS: no data on purity

Reliability : (4) not assignable
Documentation insufficient for assessment

05.02.2004 (144)

Type : LD50
Value : > 1000 mg/kg bw
Species : rabbit
Strain : no data
Sex : no data
Number of animals :
Vehicle : no data
Doses : no data
Method : other: no further information
Year : 1955
GLP : no
Test substance : other TS: no data on purity

Reliability : (4) not assignable
Documentation insufficient for assessment
05.02.2004 (8)

Type : LD0
Value : = 2000 mg/kg bw
Species : rabbit
Strain : no data
Sex : no data
Number of animals : 1
Vehicle : other: no data
Doses : 1000, 2000 mg/kg bw
Method : other: no data
Year : 1954
GLP : no
Test substance : other TS: no data on purity

Result : Animal dosed with 1000 mg/kg bw survived. Animal dosed with 2000 mg/kg bw died after 2 days. No further data
Reliability : (4) not assignable
Documentation insufficient for assessment
17.03.2004 (141)

Type : LD50
Value : = 800 mg/kg bw
Species : cat
Strain : no data
Sex : no data
Number of animals :
Vehicle : no data
Doses : no data
Method : other: no further information available
Year : 1986
GLP : no data
Test substance : other TS: no data on purity

Reliability : (4) not assignable
Insufficient for assessment
05.02.2004 (145)

Type : LD50
Value : < 100 mg/kg bw
Species : guinea pig
Strain : no data
Sex : no data

Number of animals	:	
Vehicle	:	no data
Doses	:	no data
Method	:	other: no further information available
Year	:	1968
GLP	:	no
Test substance	:	other TS: no data on purity
Reliability	:	(4) not assignable Insufficient for assessment

05.02.2004 (146)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	LC50
Value	:	> 210 mg/m³
Species	:	rat
Strain	:	other: albino
Sex	:	male
Number of animals	:	6
Vehicle	:	other: air
Doses	:	0.21 mg/l
Exposure time	:	1 hour(s)
Method	:	other: 6 rats were exposed for 1 h, at room temperature and total air flow of 10.01 ppm. Signs of intoxication were recorded, and gross autopsy was performed.
Year	:	1970
GLP	:	no
Test substance	:	other TS: no data on purity, melting point: 130.8° C
Result	:	The only sign of intoxication was lacrimation, which was observed 0-15 min after start of the exposure and ended at the same day, no deaths occurred. Gross autopsy revealed no significant findings.
Reliability	:	(4) not assignable Industrial Biotest Laboratories (IBT) unreliable test institute

26.11.2004 (136)

Type	:	other: LC
Value	:	< 100 mg/m³
Species	:	rat
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	no data
Doses	:	no data
Exposure time	:	2.5 hour(s)
Method	:	other: no further information available
Year	:	1982
GLP	:	no data
Test substance	:	other TS: no data on purity
Result	:	Inhalation: LC rat < 100 mg/m3 after 2.5 h of exposure; no further data
Reliability	:	(4) not assignable Documentation insufficient for assessment

23.11.2004 (143)

Type	:	LC50
Value	:	> 80 mg/m³

Species	:	other: rat, mouse, guinea pig
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	no data
Doses	:	no data
Exposure time	:	6 hour(s)
Method	:	other: not stated
Year	:	1975
GLP	:	no
Test substance	:	other TS: no data on purity
Reliability	:	(4) not assignable Information insufficient for assessment, secondary literature

17.03.2004 (147)

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD50
Value	:	> 10000 mg/kg bw
Species	:	rabbit
Strain	:	other: albino
Sex	:	no data
Number of animals	:	5
Vehicle	:	water
Doses	:	10000 mg/kg bw as 50 % suspension in water
Method	:	other: 5 rabbits, after application of TS rabbits were wrapped, exposure time 4 hrs, symptoms were recorded, gross autopsy
Year	:	1970
GLP	:	no
Test substance	:	other TS: no data on purity, melting point: 130.8° C
Result	:	No signs of systemic intoxication were observed, local signs observed were mild erythema and oedema on removal of the wrappings. Recovery occurred at the same day. Gross autopsy revealed no significant findings.
Reliability	:	(4) not assignable Industrial Biotest Laboratories (IBT) unreliable test institute

26.11.2004 (136)

Type	:	LD50
Value	:	> 3160 mg/kg bw
Species	:	rabbit
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	no data
Doses	:	no data
Method	:	other: not specified
Year	:	1975
GLP	:	no
Test substance	:	other TS: no data on purity
Remark	:	Severe skin irritation was seen following 24 hour exposure. Skin changes included pale red erythema and superficial 2nd degree burns. Superficial escharosis and slight to moderate desquamation observed at 7 and 14 days.
Reliability	:	(4) not assignable

Documentation insufficient for assessment

03.03.2004 (147)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

Type	:	LD50
Value	:	= 165 mg/kg bw
Species	:	mouse
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	no data
Doses	:	no data
Route of admin.	:	i.p.
Exposure time	:	
Method	:	
Year	:	1955
GLP	:	no
Test substance	:	other TS: no data on purity
Reliability	:	(4) not assignable Documentation insufficient for assessment

22.03.2004 (8) (138)

Type	:	LD50
Value	:	< 100 mg/kg bw
Species	:	guinea pig
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	no data
Doses	:	no data
Route of admin.	:	i.p.
Exposure time	:	
Method	:	no data
Year	:	1963
GLP	:	no
Test substance	:	other TS: no data on purity
Reliability	:	(4) not assignable Documentation insufficient for assessment

03.03.2004 (139)

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	550 mg
Exposure	:	Semiocclusive
Exposure time	:	4 hour(s)
Number of animals	:	6
Vehicle	:	no data
PDII	:	
Result	:	slightly irritating
Classification	:	
Method	:	OECD Guide-line 404 "Acute Dermal Irritation/Corrosion"
Year	:	1983
GLP	:	no data

Test substance : other TS: 99.8 %, physical form: flakes

Result : Scores:

Rabbit nr:	1 2 3 4 5 6
Sex:	m m m f f f
1 hour	
erythema	1 1 1 1 0 1
oedema	0 0 0 0 0 0
24 hour	
erythema	2 1 1 1 0 1
oedema	1 0 0 2 0 0
48 hour	
erythema	2 1 0 2 0 1
oedema	1 0 0 2 0 0
72 hour	
erythema	1 1 0 1 0 1
oedema	1 0 0 1 0 0
5, 6, 8-12, and 14 days:	
erythema	0 0 0 0 0 0
oedema	0 0 0 0 0 0

Dermal irritation index (1, 24, 48, and 72 h). 1.21
Phthalic anhydride was named slightly irritating

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
01.03.2006 (148)

Species : rabbit
Concentration : 500 mg
Exposure : Semiocclusive
Exposure time : 24 hour(s)
Number of animals : 2
Vehicle : other: moisted with water
PDII :
Result : not irritating
Classification :
Method : other: 1 male + 1 female New Zealand White rabbit, ear, 500 mg/rabbit moisted with water, fixed with a tape, exposure time: 24 h, then cleaning with water, soap and oil, post exposure observation time: 14 days
Year : 1978
GLP : no
Test substance : other TS: no data on purity or physical form or test compound

Result : both rabbits: no reaction was observed (score: 0)
Reliability : (2) valid with restrictions
Limited documentation, no data on compound purity, animals were dosed at the ear for 24 hours
Flag : Critical study for SIDS endpoint
28.04.2006 (149)

Species : rabbit
Concentration : 500 mg
Exposure : Semiocclusive
Exposure time : no data
Number of animals : 6
Vehicle : other: moisted with water
PDII :
Result : moderately irritating
Classification :

Method	:	other: 500 mg dry powder moisted with 0.1 ml water was applied on the intact and abraded skin of rabbits respectively; reading after 24, and 72 hours
Year	:	1970
GLP	:	no
Test substance	:	other TS: no data on purity, melting point: 130.8° C
Result	:	intact skin: 24 h reading: erythema: 6/6 rabbits (score 1), oedema: 6/6 rabbits (score 1); 72 h reading: erythema: 0/6 rabbits, oedema: 0/6 rabbits abraded skin: 24 h reading: erythema: 6/6 rabbits (score 1), oedema: 6/6 rabbits (score 1); 72 h reading: erythema: 0/6 rabbits, oedema: 0/6 rabbits
Reliability	:	(4) not assignable Industrial Biotest Laboratories (IBT) unreliable test institute

26.11.2004 (136)

Species	:	rabbit
Concentration	:	500 mg
Exposure	:	
Exposure time	:	
Number of animals	:	6
Vehicle	:	
PDII	:	
Result	:	not irritating
Classification	:	
Method	:	other: based on OECD Guide-line 404
Year	:	1985
GLP	:	no data
Test substance	:	other TS: no data on purity
Method	:	Animals: adult male and female New Zealand rabbits, weighing 2-4 kg, individual housing, except during exposure feed and drinking water ad libitum; dorsal and lateral parts of the trunk were shorn 15-24 hours before treatment 0.5 g/animal was applied to a gauze patch and then fixed on the prepared skin areas as follows: 1. semi-occlusive dressing: exposure time: 1 hour and 4 hours respectively 2. occlusive dressing: exposure time: 1 hour and 4 hours respectively After removal of the patches treated skin areas were rinsed with water and dried. Readings were performed at 1, 24, 48, 72 hours and 7 days after removal of the patch
Result	:	The substance revealed no irritational effects after both occlusive and semi-occlusive, dosing.
Reliability	:	(2) valid with restrictions Tests were based on OECD guidelines, limited documentation, no data on purity of phthalic anhydride

22.03.2004 (150)

Species	:	rabbit
Concentration	:	no data
Exposure	:	no data
Exposure time	:	no data
Number of animals	:	
Vehicle	:	no data
PDII	:	

Result	:	irritating
Classification	:	
Method	:	other: no further information available
Year	:	1984
GLP	:	no data
Test substance	:	other TS: no data on purity
Reliability	:	(4) not assignable Secondary literature, no primary data

03.03.2004 (151)

Species	:	rabbit
Concentration	:	500 mg
Exposure	:	Semiocclusive
Exposure time	:	24 hour(s)
Number of animals	:	6
Vehicle	:	other: moisted with saline
PDII	:	1.5
Result	:	slightly irritating
Classification	:	
Method	:	other
Year	:	1986
GLP	:	no data
Test substance	:	other TS: no data on purity
Method	:	Per animal four test sites, two on each side of the rabbits back were utilized for administration. Separate animals were not used for an untreated control group. Test substance, positive control (1% sodium lauryl), negative control, and solvent controls were applied to the skin (surface 1 x 1 inch, ca. 2.5 x 2.5 cm = 6,25 cm2), and covered with a gauze patch for 24 hours. Animals were scored at 25, 48, and 72 hours.
Result	:	Skin response was classified "mild" and PDII was 1.5; no further data
Reliability	:	(2) valid with restrictions Limited documentation, no data on compound purity, no data on individual animals

22.03.2004 (152)

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Dose	:	50 other: mg
Exposure time	:	
Comment	:	
Number of animals	:	2
Vehicle	:	
Result	:	moderately irritating
Classification	:	
Method	:	other: 1 male and 1 female New Zealand White rabbit, 50 mg/rabbit was applied into the conjunctival sac of one eye of each rabbit, observation time: 7 days, evaluation according Draize
Year	:	1978
GLP	:	no
Test substance	:	other TS: no data on purity or physical form of test compound
Result	:	Scores: rabbit1 - rabbit2 cornea (maximal score 4):

1h: 1 - 1
24h: 1 - 1
day 2: 1 - 0
day 7: 0- 0
transitional slight cloudiness of the cornea
Iris (maximal score: 2):
1h: 1 - 1
24 h and later: 0 - 0
conjunctiva, redness (maximal score 3):
1h: 2 - 2
24h: 1 - 2
day 2: 1 - 1
day 7: 1 - 1
conjunctiva, swelling (maximal score 4):
1h: 2 -1
24 h and later: 0 - 0
lacrimation:
1h: 1 - 1
24 h and later day 14: 0 - 0
The cornea was temporary cloudy. The observed effects were not fully reversible during the 7 days observation period

Reliability : (2) valid with restrictions
Observation time 7 days, short documentation, low dose 50 mg
Flag : Critical study for SIDS endpoint
04.05.2006 (149)

Species : rabbit
Concentration : undiluted
Dose : 100 other: mg
Exposure time : unspecified
Comment :
Number of animals : 6
Vehicle : none
Result : irritating
Classification :
Method : other: 100 mg dry powder was applied into the conjunctival sac of one eye of each of 6 rabbits, reading according to standard US method (Code of Federal Registrations, 1981) was performed 24, 48 and 72 post application of TS
Year : 1970
GLP : no
Test substance : other TS: no data on purity, melting point: 130.8° C

Result : 24 hr-reading:
cornea: 5/6 rabbits, score: 40, 1/6 rabbit score: 80; iris: 6/6 rabbits, score: 10; conjunctivae: 2/6 rabbits, score: 16, 3/6 rabbits, score: 14, 1/6 rabbits, score: 12
48 hr-reading:
cornea: 2/6 rabbits, score: 30, 1/6 rabbits, score: 40, 1/6 rabbits, score: 60, 2/6 rabbits, score 80; iris: 6/6 rabbits, score: 10; conjunctivae: 1/6 rabbit, score: 10, 3/6 rabbits, score: 14, 2/6 rabbits, score: 16
72 hr-reading
cornea: 2/6 rabbits, score: 30, 2/6 rabbits, score: 60, 2/6 rabbits, score: 80; iris 6/6 rabbits, score: 10; conjunctivae: 1/6 rabbit, score: 12, 2/6 rabbit, score: 16, 3/6 rabbit, score: 14

Mean scores:
24 h: 71/110, 48 h: 77.3/110, 72 h: 81/110
Reliability : (4) not assignable
Industrial Biotest Laboratories (IBT) unreliable test institute

26.11.2004 (136)

Species	:	rabbit
Concentration	:	no data
Dose	:	other: no data
Exposure time	:	
Comment	:	
Number of animals	:	
Vehicle	:	no data
Result	:	
Classification	:	
Method	:	other: not specified
Year	:	1975
GLP	:	no
Test substance	:	other TS: no data on purity
Remark	:	Result: extremely irritating
Reliability	:	(4) not assignable Documentation insufficient for assessment

17.03.2004 (147)

Species	:	rabbit
Concentration	:	undiluted
Dose	:	100 other: mg
Exposure time	:	
Comment	:	
Number of animals	:	9
Vehicle	:	none
Result	:	irritating
Classification	:	
Method	:	other: 9 animals were dosed (3 irrigated after 20 s; 6 nonirrigated)
Year	:	1986
GLP	:	no data
Test substance	:	other TS: no data on purity, melting point: 130.8° C
Result	:	Animals were scored according to Draize at 1 hour, 1, 2, 3, 4, and 7 days, and if irritation persists also on day 10. Mean Draize score at 24 hours = 59.2; no further data on phthalic anhydride.
Reliability	:	(2) valid with restrictions Poor documentation, no data on individual animals

01.03.2006 (152)

5.3 SENSITIZATION

Type	:	Guinea pig maximization test
Species	:	guinea pig
Concentration	:	1st: Induction .1 % intracutaneous 2nd: Induction 25 % occlusive epicutaneous 3rd: Challenge 10 % occlusive epicutaneous
Number of animals	:	
Vehicle	:	other: acetone /polyethylene glycol 400 = 70:30
Result	:	sensitizing
Classification	:	
Method	:	other: according to OECD Guide-line 406, see also freetext ME
Year	:	1992
GLP	:	no data
Test substance	:	other TS: purity >98%

Method	:	test animals: guinea pigs (weight at the start of the study: ca. 350 g) number not mentioned A preliminary irritation test was performed to determine the concentrations suitable for induction of sensitization and sensitization challenge (no data given). test procedure: Induction: 6 intradermal injections in the shoulder region Sensitization was boosted after 6-8 days by a 48 hour occlusive patch over the injection site. Challenge: 12 to 14 days later animals were challenged by a 24-h occlusive patch on 1 flank at the maximum non-irritant concentration. Animals were scored 24 and 48 h after removal of patch for erythema and oedema. Response was quantified as % of test animals judged to be positive at 24 and/or 48 h Positive controls: cinnamic aldehyde, and mercaptobenzothiazole gave the expected results.
Result	:	90 % of the tested guinea pigs were judged to be positive. Classification: extreme (no further details given)
Reliability	:	(2) valid with restrictions No solvent control, details of the reading not given, number of animals not given, poor documentation
Flag	:	Critical study for SIDS endpoint
17.03.2004		(153)

Type	:	Mouse local lymphnode assay
Species	:	mouse
Number of animals	:	
Vehicle	:	other: acetone + olive oil
Result	:	sensitizing
Classification	:	
Method	:	other: LLNA; control compounds (cinnamic aldehyde and mercaptobenzothiazole) gave the expected results.
Year	:	
GLP	:	no data
Test substance	:	other TS: no data on purity
Result	:	Phthalic anhydride has sensitizing potential in the LLNA.
Reliability	:	(2) valid with restrictions Limited documentation
22.03.2004		(154) (155) (156) (157) (158) (159)

Type	:	other: Mouse Ear Swelling Test (MEST)
Species	:	mouse
Concentration	:	1st: Induction 10 % open epicutaneous 2nd: Challenge 10 % open epicutaneous 3rd:
Number of animals	:	
Vehicle	:	other: acetone
Result	:	sensitizing
Classification	:	
Method	:	other: MEST see also freetext ME
Year	:	1986
GLP	:	no data
Test substance	:	other TS: purity no data

Method	:	test animals: 10-15 mice (males and females) test procedure: day 0: Fur of abdomen is clipped, intradermal injection of Freund's Complete Adjuvant, abdominal skin is tape stripped, application of TS: 100 ul of a 10 % solution in acetone or vehicle alone (acetone), abdominal skin site is dried rapidly. Day 1, 2, 3: abdominal skin is tape stripped, topical application of TS or vehicle, abdominal skin site is dried rapidly. Day 10: topical application of TS (10 % solution) to one ear, topical application of vehicle to contralateral ear, both ears were dried rapidly. Day 11, 12: ear thickness measurement of test and control ears with micrometer
Result	:	Phthalic anhydride increased ear thickness by 6 % (105-106 %).
Reliability	:	(2) valid with restrictions Method not validated
17.03.2004		(160) (161)

Type	:	Buehler Test
Species	:	guinea pig
Concentration	:	1st: other: no data 2nd: 3rd:
Number of animals	:	
Vehicle	:	no data
Result	:	sensitizing
Classification	:	
Method	:	other: according: Bühler, Arch. Dermatol. 91, 171 1965 : no further details given
Year	:	1988
GLP	:	no data
Test substance	:	other TS: no data on purity
Reliability	:	(4) not assignable A survey of test results from 52 substances using different test methods
17.03.2004		(162)

Type	:	Intracutaneus test
Species	:	guinea pig
Number of animals	:	
Vehicle	:	
Result	:	sensitizing
Classification	:	
Method	:	other: see freetext ME
Year	:	1940
GLP	:	no
Test substance	:	other TS: no data on purity
Method	:	Three or more albino guinea pigs were injected on the back twice a week, intracutaneously, with 0.05 cc of a 0.1 % phthalic anhydride in olive oil (phthalic acid anhydride had to be dissolved at first in dioxane). Then the treatment was continued for 2 or 2.5 weeks. The animals were tested not more than 2 weeks after the last treatment. No further details reported.
Reliability	:	(4) not assignable Test description insufficient for assessment
22.03.2004		(163)

Type	:	other:
Species	:	human
Remark	:	There are numerous studies available of respiratory allergy caused by phthalic anhydride. Bronchial asthma was diagnosed in ca. 14-18 % of factory workers, and rhinitis or conjunctivitis in ca. 70 %. In some patients with bronchial asthma, the level of specific IgE and IgG were significantly increased.
Reliability	:	(2) valid with restrictions No data on purity of the compound in most of the publications
17.03.2004		(164) (165) (166) (167) (168) (169) (170) (171) (172) (173) (174) (175) (176) (132) (177)

Type	:	Intracutaneus test
Species	:	monkey
Number of animals	:	4
Vehicle	:	
Result	:	
Classification	:	
Method	:	other: see ME
Year	:	1988
GLP	:	no data
Test substance	:	other TS: purity approx. 100%
Method	:	Four groups of four Macaea fascicularis monkeys were administered 10 consecutive weekly s.c. injections of 2 mg aluminium hydroxide plus: group 1: 200 ug of phthalic anhydride monkey serum albumin (PA-MSA); group 2: 200 ug of phthalic anhydride dissolved in EtOH; group 3: EtOH; group 4: monkey serum albumin. Direct intracutaneous tests were performed at biweekly intervals. IgE and IgG were determined according to the ELISA and RAST methods at 2-weekly intervals.
Result	:	The prevalence of cutaneous sensitivity to PA-MSA was significantly greater after 4, 6, 8, and 10 weeks ($p < 0.05$) compared with the other groups. Significantly elevated ($p < 0.01$) PA-MSA-specific IgG was observed in group 1. No significant changes in PA-MSA RAST or total IgE were observed in any group.
Reliability	:	(2) valid with restrictions No GLP, number of animals low
04.03.2004		(178)

Type	:	Mouse local lymphnode assay
Species	:	mouse
Number of animals	:	
Vehicle	:	other: aceton : olive oil
Result	:	sensitizing
Classification	:	
Method	:	other: LLNA
Year	:	2000
GLP	:	no data
Test substance	:	other TS: no data on purity
Method	:	Groups of 3 CBA/Ca mice (males and females, age of 8-12 weeks) were pretreated with 1% SDS (sodium dodecyl sulphate) one hour before exposing the animal to 25 µl of test solution in vehicle or vehicle alone on both ears daily for three days. Application of 1 % SDS and the test chemical generally resulted in a increased response compared to the test chemical alone (data not shown). Phthalic anhydride concentration used: 0, 0.25, 1, 2.5, 10, and 25%.

phthalic anhydride was solved in acetone/olive oil.

5 days after the first topical application mice were killed and the draining auricular lymph nodes were excised and pooled for each animal. A single cell suspension of lymph node cells were prepared, cells were cultured in the presence of [3H]TdR, and incorporation of the radioactivity was measured.
Chemicals that elicit a stimulation index (SI) of 3 or more in the LLNA are considered as being sensitizers. The estimated concentration (in %) required for SI=3 (EC3) was determined as the estimated dose inducing a stimulation index of three between treated versus control animals.

Control compounds (trimellitic anhydride and other compounds) gave the expected results.

Result : EC3 value: 0.357%
Phthalic anhydride was judged on extreme sensitizer
Reliability : (2) valid with restrictions
Limited documentation, 3 animals / dose, pretreatment with 1% of SDS
Flag : Critical study for SIDS endpoint
01.03.2006 (179)

Type : Mouse local lymphnode assay
Species : mouse
Number of animals :
Vehicle : other: acetone : olive oil = 4:1
Result : sensitizing
Classification :
Method : other: LLNA similar to OECD TG 429
Year : 1992
GLP : no data
Test substance : other TS: purity >98%

Method : Groups of 4 CBA/Ca mice (males and females, age of 8-12 weeks) were treated by daily topical application of 25 ul solution containing 2.5, 5, 10 % phthalic anhydride in acetone/olive oil for 3 consecutive days.

4-5 days after the first topical application all mice were injected with radio-labelled methylthymidine via tail vein. After 5 hours the mice were killed and the draining auricular lymph nodes were excised and pooled for each group. A single cell suspension of lymph node cells were prepared.
A chemical was regarded as a sensitizer in the LLNA if at least one concentration of the chemical resulted in a threefold or greater increase of labelled thymidine incorporation compared with control values.

Control compounds (cinnamic aldehyde and mercaptobenzothiazole) gave the expected results.

Result : Ratio of test to control lymphocyte proliferation:
2.5%: 26
5%: 21.5
10%: 20,9
Sensitizer
Reliability : (2) valid with restrictions
No GLP, test similar to OECD TG 429, dpm/node not given
Flag : Critical study for SIDS endpoint
22.03.2004 (153)

Type : other:
Species : rabbit
Number of animals : 2
Vehicle : other: rabbit-serum albumin (RSA)

Result	:	
Classification	:	
Method	:	other: see ME
Year	:	1997
GLP	:	no data
Test substance	:	other TS: no data on purity given
Method	:	Phthalic anhydride was conjugated with RSA. PA-RSA was solubilized (1 mg/ml) in 0.75 ml Freund's Adjuvant Complete. The mixture was s.c. injected weekly for 12-13 weeks and IgG specific antibodies were detected.
Result	:	Two types of specific IgG were produced in rabbits after PA-RSA immunization
Reliability	:	(3) invalid Test compound phthalic anhydride conjugated to RSA
22.03.2004		(180)
Type	:	other:
Species	:	mouse
Number of animals	:	10
Vehicle	:	other: acetone: olive oil = 4:1
Result	:	
Classification	:	
Method	:	
Year	:	
GLP	:	no data
Test substance	:	other TS: no data on purity
Method	:	Groups of BALB/c mice (n=5-10) received 50 ul of a 1 M solution of the test chemical in acetone-olive oil (4:1) on each shaved flank. 5-7 days later 25 ul of the same solution diluted 1:1 with the vehicle were applied to the dorsum of both ears. Mice were sacrificed by cardiac puncture and serum was prepared. IgE and cytokine concentrations were measured by ELISA.
Result	:	Phthalic anhydride increased IgE concentrations in the blood, significantly. In summary: phthalic anhydride elicited responses characteristic of Th2 cell activation.
22.03.2004		(155) (181) (182) (183) (184) (185)
Type	:	other: Inhalation exposure
Species	:	guinea pig
Number of animals	:	
Vehicle	:	
Result	:	sensitizing
Classification	:	
Method	:	
Year	:	1994
GLP	:	no data
Test substance	:	other TS: no data on purity
Method	:	Generation and analysis of phthalic anhydride dust atmospheres phthalic anhydride dust was micronized to respirable-sized particles. Chamber airflow varied between 305 and 375 L/min to generate the targeted levels of 0.5, 1.0, and 5.0 mg/m3 phthalic anhydride. The phthalic anhydride concentration in each chamber was measured at least twice during each exposure. The particle size distribution was determined. Inhalation exposure and challenge Two groups of eight Hartley smooth-haired guinea pigs each were exposed to 0.5 or 1.0 mg/m3 phthalic anhydride dust, 3 hours/day for 5 consecutive days. One group of 16 guinea pigs was exposed to filtered air, and another group of 16 guinea pigs was exposed to 5.0 mg/m3 phthalic anhydride (PA)

dust for the same amount of time. Two weeks after the last air or dust exposure, guinea pigs were challenged with phthalic anhydride dust (5 mg/m3) or phthalic anhydride guinea pig serum albumin (PA-GPSA) (2.0 mg/m3) conjugate. Animals were placed in head-out body plethysmographs. Changes in pressure and respiratory rate were monitored for each animal. Respiratory data were collected 30 minutes before the dust challenge, during the 30 minutes of dust challenge, and up to 60 minutes after the challenge. A significant immediate-onset respiratory reaction to phthalic anhydride dust challenge was defined as an increase in pressure or rate greater than three standard deviations from the mean change in the same parameters of air control animals exposed to phthalic anhydride dust.

Serum collection
Sera were collected from all study animals before the initial phthalic anhydride dust exposure (baseline) and 18 to 24 hours before respiratory challenge with phthalic anhydride dust or PA-GPSA conjugate.

Passive cutaneous anaphylaxis testing
Naive guinea pigs were shaved and depilated dorsolaterally 24 hours before passive cutaneous anaphylaxis (PCA) testing for circulating allergic antibody (IgG1a and IgE). Animals were intradermally injected with sera collected from air control and phthalic anhydride exposed animals. Four hours or 4 days later, anesthetized animals were intracardially injected with PA-GPSA or GPSA in Evans Blue Dye. IgG1a antibody titers (evaluated at 4 hours) and IgE antibody titers (evaluated at 4 days) were defined as the reciprocal of the highest dilution of serum showing visible bluing 30 minutes after intracardial injection. Confirmation of the presence of IgE antibody was made by testing untreated and heat-treated (56° C for 30 minutes) sera in the 4-day PCA test.

ELISA
Guinea pig sera were evaluated for IgG antibody to PA-GPSA or GPSA alone by an indirect ELISA.

Gross pathology and histopathology
Twenty-four hours after the phthalic anhydride challenge and the PA-GPSA challenge, air control and phthalic anhydride exposed animals were sacrificed. A gross examination of the major organs was performed on each animal. The lungs were removed, the number of hemorrhagic foci on each lung lobe was counted. The lungs were inflated with 10 % neutral buffered formalin, embedded with paraffin, sectioned to 5 µm thickness, and stained with hematoxylin and eosin for examination by light microscopy. Representative animals from the phthalic anhydride-exposed/phthalic anhydride dust-challenge group, air exposed/phthalic anhydride dust-challenge group, and air-exposed/air-challenge group were selected for microscopic examination of the lungs.

Result : Characterization of phthalic anhydride dust
phthalic anhydride dust exposure level: Mean analytical concentration (mg/m3); MMAD (µm)
0.5 mg/m3: 0.55; 3.12 +/- 2.02
1.0 mg/m3: 1.27; 3.26 +/- 2.02
5.0 mg/m3: 5.57; 3.91 +/- 2.08

Inhalation challenge with phthalic anhydride dust
Changes in respiratory rate were not significantly greater than the changes in respiratory rate measured in air control animals challenged with phthalic anhydride dust. The decrease noted in plethysmograph pressure changes was not different from those measurements taken from air control animals exposed to the same concentration of phthalic anhydride dust.

Inhalation challenge with PA-GPSA conjugate
One animal in the 0.5 mg/m3 group and four animals in the 5 mg/m3 group experienced significant and sustained increases in respiratory rate on challenge, as compared with the air control animals. The same animal in the 0.5 mg/m3 group, one animal in the 1 mg/m3 group, and three animals (two with significant increases in rate) in the 5.0 mg/m3 group experienced sustained respiratory reactions that resulted in significant increases in plethysmograph pressure, as compared with the air control animals.

ELISA
Linear regression analysis showed a highly significant dose-response relationship ($p < 0.001$) for IgG antibody.
Phthalic anhydride dust exposure level: Mean O.D. (±SE) at 1/100 serum dilution
Air contr: 0.048 ± 0.008
0.5 mg/m3: 0.230 ± 0.071
1.0 mg/m3: 0.298 ± 0.024
5.0 mg/m3: 0.692 ± 0.1061

PCA
Animals with IgG1a and IgE antibody to PA-GPSA
0.5 mg/m3: 3/8; 0/8
1.0 mg/m3: 1/8; 0/8
5.0 mg/m3: 5/8; 0/8
5.0 mg/m3: (challenged with phthalic anhydride) 1/8 ND

Thirty-eight percent (3 of 8) of the animals in the 0.5 mg/m3 group had measurable circulating IgG1a antibody in serum. Of these three animals, one had a significant respiratory reaction on inhalation challenge with conjugate. One of eight animals (13%) in the 1.0 mg/m3 exposure group had IgG1a antibody; this same animal had significant respiratory reactivity on conjugate challenge. Sixty-three percent (5 of 8) of the animals in the 5.0 mg/m3 exposure group had allergic antibody. All five animals experienced respiratory reactivity on conjugate challenge. None of the study animals had detectable IgE antibody to PA-GPSA.

Histopathology and antibody titers
Foci were observed in 8 of 8 animals in the PA dust-exposed and challenged group, with 3 of 8 having 189 foci or more (individual scores: 11, 6, 1, 365, 14, 2, 331, 189, mean value 15; mean value control group: 1). One or two lung foci were noted in 5 of 8 filtered air control/PA dust-challenged guinea pigs. No indication of hemorrhage or inflammation was noted. Alveolar hemorrhage, with accumulation of red blood cells, and a few alveolar macrophages were observed. Minimal type II cell hyperplasia was also noted.

Conclusion:
Animals exposed to and challenged with 5.0 mg/m3 PA dust had significant numbers of hemorrhagic lung foci. Those animals with the greatest number of foci had high IgG antibody activity to PA, measured by ELISA.

Reliability : (2) valid with restrictions
No GLP
Flag : Critical study for SIDS endpoint
06.03.2006 (186)

Type : other: Inhalation exposure
Species : guinea pig
Number of animals :
Vehicle :

Result : sensitizing
Classification :
Method :
Year : 1992
GLP : no data
Test substance : other TS: no data on purity

Method : Generation and analysis of PA dust atmospheres
PA dust was micronized The phthalic anhydride concentration was measured in each chamber. The particle size distribution was determined.

Inhalation exposure and challenge
Two groups of five to six guinea pigs each were exposed to dust ranging between 0.05 to 0.2 mg/m3 and 0.6 to 6 mg/m3 phthalic anhydride dust, 3 hours/day for 5 consecutive days. One group of 8 guinea pigs was exposed to filtered air. Two weeks after the last air or dust exposure, guinea pigs were challenged with phthalic anhydride guinea pig serum albumin (PA-GPSA) conjugate. Animals were placed in head-out body plethysmographs. Changes in pressure and respiratory rate were monitored for each animal. Respiratory data were collected 30 minutes before the dust challenge, during the 30 minutes of dust challenge, and up to 60 minutes after the challenge. A significant immediate-onset respiratory reaction to PA dust challenge was defined as an increase in pressure or rate greater than three standard deviations from the mean change in the same parameters of air control animals exposed to PA dust.

Serum collection
Sera were collected from all study animals before the initial PA dust exposure (baseline) and 24 hours challange

Passive cutaneous anaphylaxis testing
Naive guinea pigs were shaved and depilated dorsolaterally 24 hours before passive cutaneous anaphylaxis (PCA) testing for circulating allergic antibody (IgGla and IgE). Animals were intradermally injected with sera collected from air control and phthalic anhydride exposed animals. Four hours or 4 days later, anesthetized animals were intracardially injected with PA-GPSA or GPSA in Evans Blue Dye . IgG1a antibody titers (evaluated at 4 hours) and IgE antibody titers (evaluated at 4 days) were defined as the reciprocal of the highest dilution of serum showing visible bluing 30 minutes after intracardial injection. Confirmation of the presence of IgE antibody was made by testing untreated and heat-treated (56° C for 30 minutes) sera in the 4-day PCA test.

ELISA
Guinea pig sera were evaluated for IgG antibody to PA-GPSA or GPSA alone by an indirect ELISA.

Result : Significant responses in respiratory rate were seen in all high dose group animals, but no responses were seen at the lower exposure level. The occurence of an immunological reaction was confirmed by the detection of IgG and IgG1 antibodies in the serum of animals from the high exposure group but not in animals in the low exposure group
Reliability : (2) valid with restrictions
Phthalic anhydride exposure was expressed as a range, 0.5 - 0.2 mg/m3 and 0.6 and 6 mg/m3, respectively, due to the day-to-day difficulty in controlling the dust levels in the chambers, no MMAD given

18.03.2004 (187) (188)

Type	:	other: LLNA
Species	:	mouse
Number of animals	:	3
Vehicle	:	other: Acetone / corn oil
Result	:	
Classification	:	
Method	:	
Year	:	2001
GLP	:	no data
Test substance	:	other TS: purity not specified
Method	:	C57BL/6 mice received three applications (15% phthalic anhydride) each with a 5-day interval, with the final application for 3 consecutive days. 24 h after the last application, the local lymph nodes were excited , pooled per animal and weighted. Expression of interleucine IL-12p40 mRNA and IL-4 mRNA in the local lymph node was measured by RT-PCR. Several other compounds were used in parallel.
Result	:	The local lymph node weight increased approx. by a factor of 5. IL-12p40 mRNA level did not change compared to controls. IL-4 mRNA level were increased compared to control. The authors concluded that phthalic anhydride is a T-helper2-predominant allergen (Th2).
Reliability	:	(4) not assignable Volume of phthalic anhydride and application site not given, test system not validated

22.03.2004 (185)

Type	:	other: LLNA
Species	:	mouse
Number of animals	:	
Vehicle	:	other: Acetone / corn oil
Result	:	
Classification	:	
Method	:	
Year	:	2002
GLP	:	no data
Test substance	:	other TS: purity 99%
Method	:	Groups of five BALB/c mice received applications of phthalic anhydride or trimellitic anhydride (positive control) bilaterally on each shaved flank each. The local lymph nodes were excised , and pooled per animal. IL-4, IFN-g, IL-10, IL-12, IL-5, or IL-13 concentrations were measured by ELISA or mRNA quantification techniques.
Result	:	Proliferation of lymph nodes was stimulated. Effects observed: induced secretion/expression of: IL-5, IL-10, IL-13; and IL-4 No differences to controls (or less pronounced effects) were observed for: IL-12, and IFN-gama The authors concluded that phthalic anhydride is a Th2-predominant allergen
Reliability	:	(2) valid with restrictions Test system not validated, no statistics given (representative results were shown)

22.03.2004 (181) (189) (190) (159)

Type : other: antibody formation
Species : guinea pig
Number of animals :
Vehicle :
Result :
Classification :
Method :
Year : 1996
GLP : no data
Test substance : other TS: purity not specified

Remark : Guinea pigs were injected intradermally with cis-hexahydrophthalic anhydride, methylhydrophthalic anhydride, or methyl-hexahydrophthalic anhydride.
Provocation was performed with different anhydrides, including phthalic anhydride.

Lung resistance and IgG-ELISA inhibition tests were performed.

IgG1 induced by different organic anhydrides showed a wide range of specificity in the ELISA inhibition test.

Reliability : (4) not assignable
Phthalic anhydride was used only for challenge, not for sensitization

20.02.2004 (191)

Type : other: case reports with limited documentation
Species : human

Remark : Different sensitization reactions (asthma, rhinitis, dermatitis) have been described in humans occasionally exposed to phthalic anhydride

Reliability : (2) valid with restrictions
Limited documentation, no precise data on exposure level, mixed exposure to anhydrides and resin monomers, including phthalic anhydride

18.03.2004 (192) (193) (194) (195) (196) (197) (198) (199) (200) (201) (202) (203) (204) (205) (206) (207) (208) (209) (151) (177)

Type : other: respiratory sensitization
Species : guinea pig
Concentration : 1st: Induction other: i.p.
2nd: Challenge other: inhalation
3rd:
Number of animals :
Vehicle : no data
Result : sensitizing
Classification :
Method : other: see freetext ME
Year : 2000
GLP : no data
Test substance : other TS: no data on purity

Method : Intraperitoneal injection was used to induce an immune response, followed by inhalation challenge exposure and quantification of response using an assay for eosinophile peroxidase (EPO) in lung tissue.

Result : EPO could be detected with the known respiratory sensitizers toluene diisocyanate and phthalic acid. No further data on phthalic acid.

Reliability : (4) not assignable
Abstract only

20.02.2004 (210)

Type : other: respiratory sensitization

Species	:	guinea pig
Concentration	:	1st: Induction intracutaneous 2nd: Challenge other: inhalation 3rd:
Number of animals	:	
Vehicle	:	other:corn oil
Result	:	
Classification	:	
Method	:	other: see freetext ME
Year	:	1995
GLP	:	no data
Test substance	:	other TS: no data on purity

Method :

Test procedure:
Sensitization of guinea pigs (n=8-12) was induced by single intradermal injection of the test substance or the control material (100 µl, subscpular region, maximum concentration which produced no signs of systemic toxicity and only minimum of local irritation). A blood sample was taken from each of the treated and control animals on day 19 for serological analysis by PCA or ELISA, 3 days later the animals were challenged by an inhalation exposure (nose only, 15 min.) to the appropriate test substance or control material.
Evaluation:
the pulmonary reactions were categorized for each individual animal based on the changes in respiratory rate:
severe response:
decrease in respiration rate to 70 % or less of the normal background rate within the 15-min. challenge period.
moderate response:
increase in respiration rate to 130 % or more of the normal background rate within the 15-min. challenge period
no effect:
changes in the respiration rate within 71-129 % of the normal background rate within the 15-min. challenge period.

Experiments were conducted in two laboratories:

Laboratory 1
induction concentration:
0, 0.03 %, 0.1 %, 0.3 % in corn oil
inhalation challenge was performed by two different procedures:
a) 0, 11-29 mg/m³ of phthalic anhydride (MMDA: 3.79-4.81) in argon
b) 0, 9-48 mg/m³ of phthalic anhydride (MMDA: 0.61-18.02) in air

Laboratory 2
a) induction concentration:
0, 0.3 % in acetone in corn oil
inhalation challenge concentration: 0, 44 mg/m³ of phthalic anhydride (MMDA: 5.9-1.6) in air
b) induction concentration:
0, 0.3 % in acetone in corn oil
inhalation challenge concentration: 0, 52 mg/m³ of phthalic anhydride (MMDA: 4.7-1.6) in air

Result :

Laboratory 1
control, low, medium, high dose:
experiment a):
PCA: 0/8, 2/8, 6/8, 7/8;
pulmonary response (no-moderate-severe): 6-1-1/8, 6-1-1/8, 5-1-1/8, 4-0-4/8
experiment b)

PCA: 0/8, 7/7, 8/8;
pulmonary response: 8/8, 6-0-1/7, 5-0-3/8

Laboratory 2
controls, dosed guinea pigs
experiment a)
PCA: 1/8, 12/12;
pulmonary response (no-moderate-severe): 8/8, 12-0-0/12
experiment b)
ELISA: not tested, 3200 serum/dilution;
pulmonary response (no-moderate-severe): 6-0-1/7, 4-1-7/12

Reliability : (2) valid with restrictions
Test method not validated

22.03.2004 (211)

Type : other: study in humans
Species : human
Number of animals :
Vehicle :
Result : sensitizing
Classification :
Method :
Year : 1986
GLP : no
Test substance :

Method : Four plants for the production of reins were studied.
During 10-30 min, several times a day, paper bags containing 25 kg of flaked phthalic anhydride were cut open and emptied into chemical reactors. This work caused dust and thus inhalation during exposure. Maleic anhydride and trimellitic anhydride was sometimes used in all the plant, but to a much lesser degree, and personal respiration protection equipment was mostly used by handling the latter compound.

Phthalic anhydride levels were determined in two plants (detection limit 0.03 mg/m3)

Workers were questioned and a physical examination was performed.

Blood samples were taken and IgE level were analyzed.

Highly exposed subjects (25 workers) were skin-prick-tested, and 2 workers were submitted to bronchial provocation with phthalic anhydride.

Result : The average concentration of phthalic anhydride dust at the workplaces was given as 3-13 mg/m3, of which 40-46% was in the inspirable dust fraction.
Out of 118 workers exposed occasionally to phthalic anhydride dust for 2 months or more, 28 (24%) suffered from work-related rhinitis, 13 (11%) from chronic productive bronchitis, and 21 (28%) from work-associated asthma. Three out of eleven asthmatics had a phthalic anhydride-positive skin test, and in two subjects the presence of antibodies was demonstrated.

Reliability : (2) valid with restrictions
Limited documentation, mixed exposure

Flag : Critical study for SIDS endpoint

22.03.2004 (84)

Type : other: study in humans
Species : human
Number of animals :

Vehicle :
Result : sensitizing
Classification :
Method :
Year : 1991
GLP : no
Test substance :

Method : Two plants producing resins were studied. During 5-30 min and 0-3 times per working shift, paper bags containing flasked phthalic anhydride were cut open and manually emptied into chemical reactors. Personal respiratory protective devices were used only irregularly.

The workers were exposed to several anhydrides; maleic anhydride, isophthalic anhydride, and trimellitic anhydride were sometimes used in both plants but "to a much lower degree".

Individual exposure to phthalic anhydride in air was determined.

A group of 23 men (mean age 35 years; average exposure for 7 years) regularly exposed to phthalic anhydride during reactor loading activities were investigated. A control group of 18 men employed in a municipal engineering department, matched for age and smoking habits, served as controls.

The subjects were interviewed about symptoms of conjunctivitis, rhinitis, asthma, chronic bronchitis, and smoking habits.

Skin prick tests were performed using 13 allergens as well as a conjugate of phthalic anhydride to HSA.

Total serum IgE and phthalic anhydride specific IgE and IgG were determined

Lung function tests were performed

Result : Time-weighted average air level during loading of 6.6 mg/m3 were reported (TWA other tasks: < 0.05 mg/m3, maleic anhydride 0.6 mg/m3).

Work-related respiratory symptoms were more prevalent in exposed subjects compared to control subjects (eyes 48% vs 6%, nose, 39% vs 0%) but the control group exhibited more symptoms of nonspecific bronchial hyperreactivity (44% vs 13%). Two exposed subjects had work-related asthma and one control subject had asthma which was considered not to be work-related.

The exposed group had significantly higher total serum IgE levels (32 vs 15 kIU/l), although phthalic anhydride-specific IgE levels were similar for both groups (1.2 vs 1.3 RAST ratio). Specific IgG levels were significant greater in the exposed group (0.21 vs 0.12 D).

Lung function tests did not show any difference between the two groups.

workers exposed to an airborne phthalic anhydride dust concentration of about 6,6 mg/m3 (2-6 hour TWA) complained of conjunctivitis.

Reliability : (2) valid with restrictions
Mixed exposure
Flag : Critical study for SIDS endpoint
22.03.2004 (85)

Type : other: study in humans

Species	:	human
Number of animals	:	
Vehicle	:	
Result	:	sensitizing
Classification	:	
Method	:	
Year	:	1988
GLP	:	no
Test substance	:	

Method : Two plants producing resins were studied. During 5-30 min and 0-3 times per working shift, paper bags containing flasked phthalic anhydride were cut open and manually emptied into chemical reactors. Personal respiratory protective devices were used only irregularly.

The workers were exposed to several anhydrides; maleic anhydride, isophthalic anhydride, and trimellitic anhydride were sometimes used in both plants but "to a much lower degree" than phthalic anhydride.

Individual exposure to phthalic anhydride in air was determined.

A group of 31 and 29 men were studied in plant A and B, respectively. 28 subjects had been heavily exposed (including loading of the reactors), 25 subjects were slightly exposed. Mean employment time 12 years. A control group of 22 men employed in food-processing factory, matched for age and smoking habits, served as controls.

The subjects were interviewed about symptoms of conjunctivitis, rhinitis, asthma, chronic bronchitis, and smoking habits.

Skin prick tests were performed using 15 allergens as well as a conjugate of phthalic anhydride to HSA.

Total serum IgE, IgA, IgG, and IgM level were determined were determined.

Result : Time-weighted average air level during loading of 6.6 mg/m3 were (6.1 and 6.8 mg/m3 in factory A and B respectively)..

Work-related respiratory symptoms were more prevalent in the heavily exposed group (conjunctivitis: 16/35 (46%) rhinitis 14/35 (40%). The corresponding figures were 20% and 5% in the 25 slightly exposed workers. 5/35 heavily exposed workers reported asthma at some occasion and 6/35 (17%) had chronic bronchitis (4% in the control group).

No difference in total IgE, IgG, and IgM nor phthalic anhydride specific IgE, IgM. One worker with asthma had an increased specific IgE level. Subjects with symthoms did not differ from subjects without symptomes in total IgE, IgM, IgA, or phthalic anhydride specific IgE, IgM. Subjects with rhinoconjunctivitis had lower total IgG than other workers. The subjects with asthma had higher values for speecific IgG than asymthotic subjects. 4 Subjects had specific IgG of subclass IgG4.3/4 subjects had asthma, and one had rhinitis.

The authors reported that the clinical symptoms seemed to appear after repeated peak exposure to phthalic anhydride concentrations of about 6 mg/m3. In more than one third of the workers exposed to such concentrations increased levels of specific IgG directed against phthalic anhydride were found.

Workers exposed to an airborne phthalic anhydride dust concentration of

about 6,6 mg/m3 (2-6 hour TWA) complained of conjunctivitis.
Reliability : (2) valid with restrictions
Mixed exposure
Flag : Critical study for SIDS endpoint
22.03.2004 (212)

5.4 REPEATED DOSE TOXICITY

Type : Sub-acute
Species : rat
Sex : male
Strain : no data
Route of admin. : inhalation
Exposure period : 14 d
Frequency of treatm. : 4 h/d
Post exposure period : no
Doses : 10 mg/l
Control group : no
Method : other: 4 g phthalic anhydride was heated up to 110-150° C, 2 rats were used
Year : 1954
GLP : no
Test substance : other TS: data on purity not specified

Result : Animals were covered with phthalic anhydride dust after exposure. Slightly reduced breathing.
Reliability : (4) not assignable
No GLP, no histopathology
18.01.2005 (141)

Type : Sub-acute
Species : rat
Sex : no data
Strain : no data
Route of admin. : inhalation
Exposure period : several days
Frequency of treatm. : 4 h/d
Post exposure period : no
Doses : 10 mg/l
Control group : no data specified
Method : other: no data
Year : 1967
GLP : no
Test substance : other TS: no data on purity

Remark : No. of animals: no data.
Result : Exposure produced 25 % fatality.
Reliability : (4) not assignable
Secondary literature
18.03.2004 (137)

Type : Sub-acute
Species : rat
Sex : male
Strain : no data
Route of admin. : oral feed
Exposure period : 28 days
Frequency of treatm. : daily

Post exposure period	:	no
Doses	:	0, 250, 1000, 3800 ppm = 0, 20.7, 82.2, 319.6 mg/kg bw/d
Control group	:	yes, concurrent no treatment
NOAEL	:	= 3800 ppm
Method	:	other: 10 male rats/group, TS was blended with the basal diet. Diets were prepared fresh weekly, control rats received basal diet only. Body weight, food consumption and weights of liver, kidney, adrenals and testes were recorded.
Year	:	1970
GLP	:	no
Test substance	:	other TS: no data on purity, melting point:130.8°C
Result	:	Clinical observations: 1000 ppm: one rat died on day 14; death was not related to ingestion of phthalic anhydride. No untoward reactions were observed during the study. Body weight gain and feed consumption was comparable in all groups. Pathological examination: Organ to body weight ratio for liver, kidneys, adrenals and testes revealed no differences between the groups. No gross lesions were noted among any test rats when compared to control rats
Reliability	:	(4) not assignable Industrial Biotest Laboratories (IBT) unreliable test institute

26.11.2004 (136)

Type	:	Sub-chronic
Species	:	rat
Sex	:	male/female
Strain	:	Fischer 344
Route of admin.	:	oral feed
Exposure period	:	7 weeks
Frequency of treatm.	:	daily
Post exposure period	:	1 week
Doses	:	0, 6200, 12500, 25000, 50000 ppm
Control group	:	yes, concurrent no treatment
Method	:	other: see freetext ME
Year	:	1979
GLP	:	no data
Test substance	:	other TS: purity 98.8 %
Method	:	ANIMALS AND DOSING 5 males and 5 females/group as 4-week old weanlings Animals were dosed for 7 weeks, followed by one week of further observation. ANIMAL MAINTENANCE Polycarbonate cages; sterilizable lab meal ad libitum replenished at least 3 times per week; water acidified to pH=2.5 ad libitum; air in the animal room: 22-24°C, relative humidity: 45-55 %, 15 changes of room air per hour; fluorescent lighting on a 12 hour-per day cycle TYPE AND FREQUENCY OF OBSERVATION Each rat was weighed twice per week. NECROPSY AND HISTOLOGICAL EXAMINATION: At the end all animals were killed using CO2 inhalation and necropsied.
Remark	:	Dose-finding study for a carcinogenicity study
Result	:	No animal died during subchronic test. Mean body weight at week 7 as percent of control (dose: m/f): 6200 ppm: 90/95 %, 12500: 95/93 %, 25000 ppm: 92/91 %, 50000 ppm: 71/76 % Lowest dose at which histopathologic findings were observed in males and females was 25000 ppm. At this dose, trace amounts of centrilobular

cytoplasmic vaculation were seen in the livers of four males, tissues were essentially normal in both males and females at 50000 ppm.

Reliability : (2) valid with restrictions
Dose-finding study, poor documentation

Flag : Critical study for SIDS endpoint

22.03.2004 (213)

Type	:	Chronic
Species	:	rat
Sex	:	male/female
Strain	:	Fischer 344
Route of admin.	:	oral feed
Exposure period	:	105 week
Frequency of treatm.	:	daily
Post exposure period	:	no
Doses	:	7500, 15000 ppm = ca. 500, 1000 mg/kg bw/d
Control group	:	yes, concurrent no treatment
Method	:	other: see freetext ME
Year	:	1979
GLP	:	no data
Test substance	:	other TS: purity 98.8 %

Method :

ANIMALS
Age: 6 weeks
50 males and 50 females/dose group
20 males and 20 females as controls
DOSING
Test diets containing phthalic anhydride were prepared fresh every 1 to 1-1/2 weeks at appropriate doses. The diets were routinely stored at 5 degree Celsius until used.
Analytical analyses indicated that when phthalic anhydride was mixed with Lab Meal at a concentration of 15,000 ppm and stored at room temperature for 2 weeks, the loss was 2.59% (372 ppm) per day.
ANIMAL MAINTENANCE
Polycarbonate cages; sterilizable lab meal ad libitum replenished at least 3 times per week; water acidified to pH=2.5 ad libitum; air in the animal room: 22-24° C, relative humidity: 45-55 %, 15 changes of room air per hour; fluorescent lighting on a 12 hour-per day cycle
TYPE AND FREQUENCY OF OBSERVATION
Each rat was weighed once per month, daily observations for sick, tumour bearing and moribund animals, twice daily checked for deaths
NECROPSY AND HISTOLOGICAL EXAMINATION:
At the end all animals were killed using CO2 inhalation and necropsied; gross and microscopic examination of:
skin, lungs and bronchi, trachea, bone marrow (femur), spleen, lymph nodes (mesenteric and submandibular), thymus, heart, salivary glands (patrotid, sublingual, and submaxillary), liver, pancreas, esophagus, stomach (glandular and nonglandular), small and large intestines, kidneys, urinary bladder, pituitary, adrenal, thyroid, parathyroid, pancreatic islets, testis, prostate, mammary gland, uterus, ovary, brain (cerebrum, and cerebellum), and all tissue masses. Peripheral blood smears were made for all animals, whenever possible

Result : F344 rats (50/sex/group) were fed diets containting 7500 or 15,000 ppm phthalic anhydride for 105 weeks (approx. 500 and 1,000 mg/kg bw/day). The observation that the testcompound is unstable (2.59% loss of activity per day at room temperature) has to be noted, although this is of minor relevance because the diet was prepared fresh every 1 to 1-1/2 weeks and the diet was stored at 5 degree Celsius, consequently the hydrolysis is assumed to be lower than 26%.

Body Weights and Clinical Signs
The mean body weights of the high-dose males were lower than the controls from week 13 to the end of the study, but the decrease was never more than 10%. Mean body weights of the low-dose males and both the low- and high-dose females were essentially unaffected by the test compound.

Survival
No statistical significant difference in mortality was observed in any group.
Survival male rats: high-dose group 36/50 (72 %) low-dose group 44/50 (88), control group 14/20 (70 %)
Survival female rats: high-dose group 41/50 (82 %), low-dose group 42/50 (84 %), control group 17/20 (85 %)

Pathology
Severe chronic inflammatory, degenerative, or proliferative lesions frequently seen in aged rats occurred with approx. equal frequency and severity in the dosed and control groups of animals.

Based on the reduced body-weight gain (<10 %) the NOAEL in this study was 500 mg/kg/day.

Reliability : (2) valid with restrictions
No hematology, urinalysis or clinical chemistry analyses were performed.

Flag : Critical study for SIDS endpoint

28.04.2006 (214) (215) (213) (216)

Type : Sub-acute
Species : rat
Sex : female
Strain : no data
Route of admin. : gavage
Exposure period : 9 w
Frequency of treatm. : daily
Post exposure period : no
Doses : start: 20 mg/kg bw/day; doses were doubled every week up to 4800 mg/kg bw/day in the last week; compound was dissolved in 1% Tylose
Control group : yes
Method : other: see freetext ME
Year : 1955
GLP : no
Test substance : other TS: see freetext ME

Method : Different batches of phthalic anhydride were used:
1) Phthalic anhydride (P): pure (no further data)
2) Phthalic anhydride (K2): containing up to 0.3 % naphthoquinone and 0.1 % maleic acid as impurities
3) Phthalic acid (K7): containing up to 1 % naphthoquinon and 0.5 % maleic acid as impurities.

Applied dosing volume: 1 ml/200 g rat
No. of animals: 20 female rats/test group and 20 control rats.

Doses (week 1 to 9): 20, 40, 80, 160, 320, 640, 1280, 2560, 4800 mg/kg bw/day

Parameters investigated:
body weight record: once/week
determination of number of erythrocytes and thrombocytes at the beginning and after test week 8 (10 rats/group)
all animals that died were necropsied

after termination of treatment, histopathology was performed on lungs, stomach, liver, spleen and kidneys (n = 5-6 animals)

Result : Survival rate:
control: 18/20 up to the end, (one animal was fed in the trachea, another died on sepsis)
P, K2, and K7 group:
up to and including week 7: 16/20-15/20-17/20,
up to and including week 8: 9/20-9/20-14/20,
up to and including week 9: 0/20-0/20-0/20.

Cause of death: 20 to 1200 mg/kg bw/d (up to week 7): pneumonia due to missapplication in the trachea.

Mean body weight development (start-end of week 7):
control: 226-235 g;
P: 250-230 g;
K2: 247-227 g;
K7: 230-222 g.

Thrombocytes ranging from 350000 to 850000 and erythrocytes from 5 to 8 millions (no further data)

Pathological evaluation:
ulceration of the stomach epithelium, necrosis of the kidney tubules, liver without finding, spleen, heart, lung hyperemic (details not reported).

Reliability : (2) valid with restrictions
No individual animal data, high mortality due to misapplication in the trachea, no fixed dose.

22.03.2004 (217)

Type : Sub-acute
Species : rat
Sex : no data
Strain : no data
Route of admin. : oral unspecified
Exposure period : 50 d
Frequency of treatm. : daily
Post exposure period : no
Doses : 200 mg/kg bw/d
Control group : no
Method :
Year : 1954
GLP : no
Test substance : other TS: data on purity not specified

Remark : No. of animals: 5.
Result : 1 animal died after 7 d, 2 animals were killed after 29 d, no gross pathological findings.
Reliability : (2) valid with restrictions
Poor documentation

22.03.2004 (141)

Type : Sub-acute
Species : mouse
Sex : male
Strain : other: no data
Route of admin. : inhalation
Exposure period : 14 d
Frequency of treatm. : 4 h/d

Post exposure period	:	no
Doses	:	10 mg/l
Control group	:	no
Method	:	other: 4 g of phthalic anhydride was heated up to 110-150° C, 4 mice were used
Year	:	1954
GLP	:	no
Test substance	:	other TS: data on purity not specified
Result	:	Animals were covered with phthalic anhydride dust. Slightly reduced breathing, 1 mouse died after the 2nd day, while a second one was found dead after the last day of the test.
Reliability	:	(4) not assignable No GLP, no histopathology

18.01.2005 (141)

Type	:	Sub-chronic
Species	:	mouse
Sex	:	male/female
Strain	:	B6C3F1
Route of admin.	:	oral feed
Exposure period	:	7 weeks
Frequency of treatm.	:	daily
Post exposure period	:	1 week
Doses	:	0, 6200, 12500, 25000, 50000 ppm = ca. 0, 890, 1790, 3570, 7140 mg/kg/d
Control group	:	yes, concurrent no treatment
Method	:	other: see freetext ME
Year	:	1979
GLP	:	no data
Test substance	:	other TS: purity: 98.8 %
Method	:	ANIMALS AND DOSING 5 males and 5 females/group as 4-week old weanlings Animals were dosed for 7 weeks, followed by one week of further observation. ANIMAL MAINTENANCE Polycarbonate cages; sterilizable lab meal ad libitum replenished at least 3 times per week; water acidified to pH=2.5 ad libitum; air in the animal room: 22-24° C, relative humidity: 45-55 %, 15 changes of room air per hour; fluorescent lighting on a 12 hour-per day cycle TYPE AND FREQUENCY OF OBSERVATION Each mouse was weighed twice per week. NECROPSY AND HISTOLOGICAL EXAMINATION: At the end all animals were killed using CO2 inhalation and necropsied.
Remark	:	Dose-finding study for a carcinogenicity study
Result	:	No animal died during subchronic test. Mean body weight at week 7 as percent of control (dose: m/f): 6200 ppm: 114/100 %, 12500: 113/99 %, 25000 ppm: 111/101 %, 50000 ppm: 104/99 % Histopathologic examination revealed that tissues were essentially normal in males and females at 50000 ppm. No adverse effects reported at any dose.
Reliability	:	(2) valid with restrictions Dose-finding study
Flag	:	Critical study for SIDS endpoint

23.03.2004 (213)

Type	:	Chronic
Species	:	mouse

Sex	:	male/female
Strain	:	B6C3F1
Route of admin.	:	oral feed
Exposure period	:	32 weeks, thereafter 72 weeks with lower doses
Frequency of treatm.	:	daily
Post exposure period	:	no
Doses	:	
Control group	:	yes, concurrent no treatment
Method	:	other: see freetext ME
Year	:	1979
GLP	:	no data
Test substance	:	other TS: purity 98.8 %

Method :

ANIMALS
Age: 6 weeks
50 males and 50 females/dose group
20 males and 20 females as controls
DOSING
Test diets containing phthalic anhydride were prepared fresh every 1 to 1-1/2 weeks at appropriate doses. The diets were routinely stored at 5 degree Celsius until used.
Analytical analyses indicated that when phthalic anhydride was mixed with Lab Meal at a concentration of 15,000 ppm and stored at room temperature for 2 weeks, the loss was 2.59% (372 ppm) per day.
ANIMAL MAINTENANCE
Polycarbonate cages; sterilizable lab meal ad libitum replenished at least 3 times per week; water acidified to pH=2.5 ad libitum; air in the animal room: 22-24° C, relative humidity: 45-55 %, 15 changes of room air per hour; fluorescent lighting on a 12 hour-per day cycle
TYPE AND FREQUENCY OF OBSERVATION
Each mouse was weighed once per month, daily observations for sick, tumour bearing and moribund animals, twice daily checked for deaths
NECROPSY AND HISTOLOGICAL EXAMINATION:
At the end all animals were killed using CO2 inhalation and necropsied; gross and microscopic examination of:
skin, lungs and bronchi, trachea, bone marrow (femur), spleen, lymph nodes (mesenteric and submandibular), thymus, heart, salivary glands (patrotid, sublingual, and submaxillary), liver, pancreas, esophagus, stomach (glandular and nonglandular), small and large intestines, kidneys, urinary bladder, pituitary, adrenal, thyroid, parathyroid, pancreatic islets, testis, prostate, mammary gland, uterus, ovary, brain (cerebrum, and cerebellum), and all tissue masses. Peripheral blood smears were made for all animals, whenever possible.

DOSING:
groups of 20 control or 50 treated animals of each sex were exposed via the diet at levels of 0, 25000, or 50000 ppm for the first 32 weeks of a 104 week treatment period (approx. 3570 or 7140 mg/kg bw/day). Because of excessive bodyweight loss the exposure levels in males were reduced to 12500 or 25000 ppm (approx. 1785 or 3570 mg/kg bw/day), respectively, and the doses for the females were reduced to 6250 and 12500 ppm (approx. 890 or 1780 mg/kg bw/day), respectively, for the remainder of the study.

Result :

DOSING:
The time-weighted average doses for the males were either 16346 or 32692 ppm (approx. 2340 or 4670 mg/kg bw/day), and those for the females were either 12019 or 24038 ppm (approx. 1717 or 3430 mg/kg bw/day). The observation that the testcompound is unstable (2.59% loss of activity per day at room temperature) has to be noted, although this is of minor relevance because the diet was prepared fresh every 1 to 1-1/2

weeks and the diet was stored at 5 degree Celsius, consequently the hydrolysis is assumed to be lower than 26%.

BODY WEIGHTS and CLINICAL SIGNS:
Mean body weights of dosed male and female mice were lower than those of corresponding controls throughout the bioassay, and depressions in the amount of body weight gains were dose related. Tissue masses were observed at low incidences and were common to the dosed and control groups. Fluctuation in the growth curves may be due to mortality; as the size of a group diminishes, the mean body weight may be subject to variation (data only given as figures, no precise values).

SURVIVAL and WEIGHT GAIN:
Treatment did not affect survival in either sex of mice, but there was a dose-related inhibition of weight gain; decreases at the end of the study were 12% and 25% in the males and 12% and 27% in the females.
Survival male mice: high-dose group 47/50 (94 %), low-dose group 37/50 (74 %), and control group 17/20 (85 %)
Survival female mice: high-dose group 40/50 (80 %), low-dose group 45/50 (90 %), and control group 16/20 (80 %)

PATHOLOGY:
Although NCI (1979) concluded that there were no treatment-related nonneoplastic pathological effects in the mice, examination of the incidence data by the US EPA Integrated Risk Information System (IRIS) reports significantly increased incidences of lung and kidney lymphocytosis in the low-\and high-dose males and females, chronic bile duct inflammation in the high-dose males and females and dose-related adrenal atrophy and mineralization of the thalamus in the low-\and high-dose males.

Increased lymphocytosis (incidence in controls, low-dose and high-dose groups, respectively):
Males:
lung (30%, 38%, and 61%)
kidneys (0, 30, and 76%)
Females:
lung (10, 65, 71%)
kidney (0, 46, 54%)

chronic bile duct inflammation:
Males (5, 14, 35%)
Females (50, 63, and 75%)

adrenal atrophy in males (0, 47, 83%)
mineralization of the thalamus in males (0, 36, 23%)

Thus, the LOAEL in female mice is 12,019 ppm (approx. 1717 mg/kg/day) and in males 16,346 ppm (approx. 2340 mg/kg/day)

Reliability : (2) valid with restrictions
no hematology, clinical chemistry or urinalyses performed
Flag : Critical study for SIDS endpoint
02.03.2006 (214) (215) (213) (216)

Type : Sub-acute
Species : rabbit
Sex : male
Strain : no data
Route of admin. : inhalation
Exposure period : 14 d
Frequency of treatm. : 4 h/d

Post exposure period : no
Doses : 10 mg/l
Control group : no
Method : other: 4 g of phthalic anhydride was heated up to 110-150° C, 1 rabbit was used
Year : 1954
GLP : no
Test substance : other TS: no data on purity not specified

Result : Animal was covered with phthalic anhydride dust. Slightly reduced breathing.
Reliability : (4) not assignable
No histopathology

18.01.2005 (141)

Type : Sub-acute
Species : rabbit
Sex : no data
Strain : no data
Route of admin. : inhalation
Exposure period : several days
Frequency of treatm. : 4 h/d
Post exposure period : no
Doses : 10 mg/l
Control group : no data specified
Method :
Year : 1964
GLP : no
Test substance : other TS: no data on purity

Remark : No. of animals: no data.
Result : Exposure produced 25 % fatality.
Reliability : (4) not assignable
Secondary literature

22.03.2004 (137)

Type : Sub-acute
Species : rabbit
Sex : no data
Strain : no data
Route of admin. : oral unspecified
Exposure period : no data
Frequency of treatm. : 3-4 times
Post exposure period : no data
Doses : 500 mg/kg
Control group : no data specified

Remark : No. of animals: no data.
Result : Enteritis, increased urea, death after 3-4 doses.
Reliability : (4) not assignable
Documentation insufficient for assessment

22.03.2004 (8)

Type : Sub-acute
Species : cat
Sex : male
Strain : other: no data
Route of admin. : inhalation
Exposure period : 14 d
Frequency of treatm. : 4 h/d

Post exposure period	:	no
Doses	:	10 mg/l
Control group	:	no
Method	:	other: 4 g of phthalic anhydride was heated up to 110-150° C, 1 cat was used
Year	:	1954
GLP	:	no
Test substance	:	other TS: data on purity not specified
Result	:	Animal was covered with phthalic anhydride dust. Slightly reduced breathing.
Reliability	:	(4) not assignable No histopathology

18.01.2005 (141)

Type	:	Sub-acute
Species	:	cat
Sex	:	no data
Strain	:	no data
Route of admin.	:	inhalation
Exposure period	:	7 d
Frequency of treatm.	:	6 h/d
Post exposure period	:	no
Doses	:	3.7 mg/l
Control group	:	no data specified
Method	:	
Year	:	1964
GLP	:	no
Test substance	:	
Remark	:	No. of animals: no data.
Result	:	Cats became drowsy with loss of appetite and vomited; liver and kidney injury was observed.
Reliability	:	(4) not assignable Secondary literature

22.03.2004 (137)

Type	:	Sub-acute
Species	:	cat
Sex	:	no data
Strain	:	no data
Route of admin.	:	oral unspecified
Exposure period	:	no data
Frequency of treatm.	:	up to 24 times
Post exposure period	:	no data
Doses	:	200 mg/kg
Control group	:	no data specified
Remark	:	No. of animals: no data.
Result	:	A dose of 200 mg/kg was tolerated up to 24 times without effects.
Reliability	:	(4) not assignable Documentation insufficient for assessment

22.03.2004 (8)

Type	:	Sub-chronic
Species	:	guinea pig
Sex	:	male/female
Strain	:	no data
Route of admin.	:	other: inhalation of dust

Exposure period	:	8 months
Frequency of treatm.	:	3 h/d on 4 following days, every application period was followed by a 10 d break
Post exposure period	:	no
Doses	:	see freetext ME
Control group	:	yes
Method	:	other: see freetext ME
Year	:	1956
GLP	:	no
Test substance	:	other TS: see freetext ME

Method :

Test substances:
1) Phthalic anhydride (P): pure (no further data)
2) Phthalic anhydride (K2): containing up to 0.3 % naphthoquinon and 0.1 % maleic acid as impurities
3) Phthalic acid (K7): containing up to 1 % naphthoquinon and 0.5 % maleic acid as impurities.

Applied doses:
P : 0.0085 mg/l
K2: 0.066 mg/l
K7: 0.055 mg/l
Controls: air only

Number of animals in the test groups: 8 animals/group; 20 control animals. Dead animals were replaced by animals of a further control-group 836 animals).

During each break differential blood count was examined, every 6 weeks animals were weighed.
Histopathologic examination was performed on dead animals.

Result :

Signs of intoxication:
some animals developed slight rhinitis, and some developed bradypnea. Respiration rate changed during experimental period; no lacrimation and no excitation was observed.

Body weight:
body weight increased in all groups, exception: just before death significant decrease in body weight was observed.

Mortality:
P: 5 animals, K2: 14 animals, K7: 2 animals, Controls: 3 animals. Dead animals were replaced by untreated contorl animals.

Differential blood count (mean values, control-P-K2-K7):
Basophils: 1-1-1-1; eosinophils: 4-7-5-7; juvenile leucos: none; stab cells: 0-0-0-1; segmented neutrophils: 15-21-20-19; monocytes: 2-2-2-2; lymphocytes: 78-70-71-70.

Histopathologic examination:
decedents:
P: putrid bronchitis, pleuritis and pericarditis
K2: putrid pleuritis, pericarditis and pneumonia, alveolary hyperemia
K7: hyperemia of the lungs, hyperemic abdominal cavity
controls: putrid pneumonia, pleuritis and pericarditis
all test-animals:
showed irritation of the conjunctiva and mucosa of the lungs, death and loss of superficial mucosal cells, alveolary hyperemia.

Reliability : (4) not assignable
No individual animal data, poor documentation, no analytics of test

atmosphere. Dead animals were replaced by control animals during the experiment.

18.01.2005 (217)

Type	:	Sub-acute
Species	:	guinea pig
Sex	:	female
Strain	:	no data
Route of admin.	:	other: inhalation of vapor
Exposure period	:	4 or 8 d
Frequency of treatm.	:	0.5 h/d
Post exposure period	:	no
Doses	:	see freetext ME
Control group	:	yes
Method	:	other: see freetext ME
Year	:	1956
GLP	:	no
Test substance	:	other TS: see freetext ME

Method :

Test substances:
1) Phthalic anhydride (P): pure (no further data)
2) Phthalic anhydride (K2): containing up to 0.3 % naphthoquinon and 0.1 % maleic acid as impurities
3) Phthalic acid (K7): containing up to 1 % naphthoquinon and 0.5 % maleic acid as impurities.

Applied doses:
P : 0.6145 mg/l air
K2: 1.297 mg/l air
K7: 0.9470 mg/l air
Controls: air only

Number of animals: 2 animals/group

exposure time per day: 30 min
exposure period: 2 days and 4 days, respectively

Result : all animals including the control animals showed irritation of conjunctiva, and irritation of lung mucosa probably because the temperature in the vapor inhalation chamber increased to 60 - 70 degree Celsius during the experiment.

Controls:
Respiration-rate (decrease of respiration rate, breathing/min)
C 78,5
P 60,6
K7 53,7
K2 41,2
closed eyelids, transient rhinitis.
Histopathology: no findings in the lung.

P:
abdominal respiration.
Histopathology: only 1 animal showed bronchitis, impaired mucous membranes and increased number of histiocytes.

K2:
increased lacrimation, complete eyelid closure, rhinitis, laboured breathing.
Histopathology: animals showed putrid bronchitis, hyperemia of the lungs.

K7:

signs of irritation, closed eyelids, lacrimation, slight rhinitis,
Cuogh-rate (per 30 min)
C 8
P 201
K7 1117
K2 343
Histopathology: slight bronchitis was seen.

Reliability : (4) not assignable
Temperature in the vapor inhalation chamber raised to 60 - 70 degree Celsius, no individual animal data, no analytic of test atmosphere, limited documentation

23.11.2004 (217)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Ames test
System of testing : S. typhimurium TA 98, TA 100, TA 1535, TA 1537
Test concentration : Trial1, +/-S9-mix (Hamster + Rat liver): 0.0, 3.3, 10.0, 33.0, 100.0, 333.0, 1000.0, 3333.0 ug/plate (solvent:DMSO)
Trial2, +/-S9-mix (Hamster + Rat liver): 0.0, 1.0, 3.3, 10.0, 33.0, 67.0, 100.0, 333.0, 666.0 ug/plate (solvent:DMSO)
Cycotoxic concentr. : High dose was limited by solubility and/or toxicity
Metabolic activation : with and without
Result : negative
Method : other: preincubation protocol according to Ames,1975, Mutat. Res.31, 347, S9 from male Sprague-Dawley rat and male Syrian Hamster livers, described in Haworth (1983) Environ. Mutagen. 5 [Suppl.1], 3-142, (see also freetext ME)

Year : 1985
GLP : no data
Test substance : other TS: 99 %

Method : Preparation of S-9 fraction:
Liver S9-fraction was routinely prepared from male Sprague-Dawley rats and male Syrian hamster that were injected,i.p., with Aroclor 1254. 5 days after injection, the animals were sacrificed and the livers were removed aseptically. Liver homogenates were prepared aseptically at 0-4° C: first rinsed, then minced, homogenized, centrifuged and finally distributed into freezing ampules and stored at -70° C.

Dose Setting Experiment
Phthalic anhydride was solubilized in DMSO and checked for toxicity to TA100 up to a concentration of 10 mg/plate or the limit of solubility, both in the presence and absence of S-9 mix.

Positive Controls
Positive control chemicals were tested concurrently.
-in the presence of rat and hamster S-9
-2-aminoanthracene (all strains)
-without S-9mix
-4-Nitro-o-phenylenediamine (Strain TA98)
-Sodium azide (Strain TA100 and TA1535)
-9-Aminoacridine (Strain TA1537)

Data Evaluation
A positive response was indicated by a reproducible, dose-related increase wether it was twofold over the background or not.

Remark	:	Rat and hamster liver S-9 mix
Result	:	Positive and negative controls gave the expected results, phthalic anhydride was not mutagenic in the absence and presence of S-9 extracts.
Reliability	:	(2) valid with restrictions Only 4 strains used
Flag	:	Critical study for SIDS endpoint
23.11.2004		(218) (219) (220)
Type	:	Ames test
System of testing	:	S. typhimurium TA 98, TA 100, TA 1535, TA 1537
Test concentration	:	tested quantitatively with TA 100 up to 3 umol/plate (no further information)
Cycotoxic concentr.	:	no data
Metabolic activation	:	with and without
Result	:	negative
Method	:	other: according to Ames, Mutation Res. 31, 347 (1975)
Year	:	1980
GLP	:	no data
Test substance	:	other TS: no information on purity
Reliability	:	(4) not assignable Test description insufficient for assessment
18.03.2004		(221)
Type	:	other: Chromosome aberrations test
System of testing	:	CHO cells
Test concentration	:	0, 30,100,300 µg/ml DMSO
Cycotoxic concentr.	:	dose selection was based on preliminary growth inhibition test (no details reported)
Metabolic activation	:	with and without
Result	:	negative
Method	:	other: Galloway, Environ. Mutagen. 7, 1-51 (1985) see also freetext ME
Year	:	1987
GLP	:	yes
Test substance	:	other TS: no data on purity
Method	:	Cloned Chinese hamster ovary cells (CHO-W-B1) were cultured. Test chemicals were supplied under code by the National Toxicology Program chemical repository (Radian Corp., Austin, TX) and were dissolved immediately before use in water, dimethyl sulfoxide (DMSO), ethanol, or acetone, in that order of preference. Dose Selection Originally, doses were chosen for the aberration test based on a preliminary test of cell survival 24 h after treatment Chromosome Aberration Test Cells were exposed to phthalic anhydride for 2 hours in the presence of metabolic activation (S9), and further incubated for 8-12 hours. In the tests without metabolic activation, the cells were exposed to phthalic anhydride throughout the incubation period. This treatment yielded cells in their first mitosis. Cells were collected by mitotic shake-off. Slides were stained with Giemsa and coded, and 100 cells were scored from each of the three highest dose groups having sufficient metaphases for analysis and from positive (triethylenemelamine, mitomycinC, or cyclophosphamid) and solvent control. All types of aberrations were recorded separately, but for data analysis they were grouped into categories of "simple" (breaks and terminal deletions), "complex" (exchanges and rearrangements), "other" (includes pulverized chromosomes), and "total." Gaps and endoreduplications were

recorded but were not included in the totals.

Positive Controls
without S9-mix: Mitomycin-C;
with S9-mix: Cyclophosphamide

Data Evaluation
Armitrage test: Significance of percent cells with aberrations tested by linear regression trend test versus log of the dose

Result : The highest concentration was selected as a cytotoxic level on the basis of a preliminary study.
No chromosome aberrations were recorded at any dose tested (10 - 300 µg/ml).

Without S9-mix:

Dose µg/ml	Cells no.	Percent cells with aberrations: total	simple	complex
0	100	4	3	1
30	100	5	4	1
100	100	4	4	0
300	100	5	3	2

Positive control: TEM
0.15 100 27 21 7

With S9-mix:

Dose µg/ml	Cells no.	Percent cells with aberrations: total	simple	complex
0	100	3	2	1
30	100	4	2	1
100	100	6	5	1
300	100	5	4	1

Positive control: CP
0.15 100 25 15 12

Reliability : (2) valid with restrictions
no data on compound purity, low sensitivity because only 100 metaphases scored

Flag : Critical study for SIDS endpoint

28.04.2006 (222)

Type : Sister chromatid exchange assay
System of testing : CHO cells
Test concentration : 0, 10, 30, 100, 300 ug/ml DMSO
Cycotoxic concentr. : dose selection was based on preliminary growth inhibition test (no details reported)
Metabolic activation : with and without
Result : negative
Method :
Year : 1987
GLP : yes
Test substance : other TS: no data on purity

Method : CHO cells were incubated with test compound, positive control or solvent (Dimethylsulfoxide=DMSO).

Originally, doses were chosen based on a preliminary test of cell survival 24 h after treatment.

A) Cells were incubated for 2 hours at 37 °C in the absence of S9-mix. BrdU was added and incubation was continued for 23.5 hours. Cells were washed, fresh medium containing BrdU and colcemid was added and incubation was continued for 2 to 3 hours. Cells were then collected by mitotic shake-off, fixed, air-dried and stained.
B)Cells were incubated for 2 hours at 37°C in the presence of S9-mix and 12 hours in the absence. Cells were washed and medium containing BrdU was added. Cells wee incubated for further 25,5 hours with colcemid present for the final 2 to 3 hours. Cells were collected by mitotic shake-off, fixed, air-dried and stained.

Positive Controls
in the presence of S9-mix: Cyclophosphamide
in the absence of S9-mix: Mitomycin C

Data Evaluation
Significance of relative SCEs/chromosome tested by linar regression versus log of the dose

Result : The highest concentration was selected as a cytotoxic level on the basis of a preliminary study.

Without S9-mix:

Dose	total chromos. no.	Total SCE per µg/ml	SCE cell
0	2098	1012	10,13
10	1047	472	9,47
30	1047	518	10,39
100	1051	495	9,89
300	1049	497	9,95

Positive control: TEM

0.015	1049	1607	32,14

With S9-mix:

Dose	total chromos. no.	Total SCE per µg/ml	SCE cell
0	1042	470	9,47
10	1044	459	9,23
30	1048	472	9,46
100	1048	458	9,18
300	1043	501	10,09

Positive control: CP

1	1047	1043	20,86

No significant increase in sister chromatid exchanges was observed at any concentration investigated.

Reliability : (2) valid with restrictions
No data on purity of the compound

Flag : Critical study for SIDS endpoint

01.03.2006 (222)

Type : other: Chromosome aberrations test
System of testing : CHO and RL4 cells
Test concentration : no data
Cycotoxic concentr. : no data
Metabolic activation : no data

Result	:	
Method	:	other: CHO and RL4 cells were exposed for 2 h to medium containing phthalic anhydride. Cells were treated afterwards with colcemid for 22-24 h. Metaphase arrested cells (100) were scored.
Year	:	1986
GLP	:	no data
Test substance	:	other TS: no data on purity
Result	:	Negative results, no further data
Reliability	:	(4) not assignable Documentation insufficient. No evaluation possible because details are not given

24.02.2004 (223)

Type	:	other: alkaline elution/rat hepatocyte assay
System of testing	:	primary rat hepatocytes
Test concentration	:	1, 3 or 10 mM in DMSO
Cycotoxic concentr.	:	not given
Metabolic activation	:	without
Result	:	
Method	:	other: see freetext ME
Year	:	1996
GLP	:	no data
Test substance	:	other TS: highest purity commercially available

Method : Primary rat hepatocytes were incubated in the presence of the test compound at 37° C under 5 % CO2 for 3 h.

Positive controls
1) double-strand break cells harvested from untreated control plates at the end of the 3-h incubation were irradiated on ice with 40 Gy of gamma radiation,

2) the alkaline elution assay:
cells treated with 0.2 uM aflatoxin B1 for 3 h or irradiated with 3 Gy of gamma radiation on ice.

Chemical treatments were carried out in duplicate,
solvent negative controls in quadruplicate plates.

Alkaline elution assay:
Cells were lysed in lyris-buffer (pH 9.6). The lysed cells were loaded onto polycarbonate filter columns and the DNA was sequentially eluted from the column by addition of different elution buffers.
DNA content of the different elution fractions was determined and an elution profile (slope) was established.

Cytotoxicity:
the conventional trypan blue dye exclusion assay performed after the 3-h treatment (TBDE-0), trypan blue dye exclusion performed after replating treated cells in normal, compound-free medium and incubating them for an additional 3 h to allow for recovery from cytotoxic injury (TBDE-3), cellular adenosine triphosphate (ATP) levels and potassium (K+) content, tetrazolium dye (MMT) reduction, light microscopic evaluation of cell blebbing and DNA degradation (double-strand breaks) measured by pulsed-field gel electrophoresis (PFGE).

Result : Alkaline elution assay:
very weak evidence of dose-related cytotoxicity, no
consistent dose-related increases in the alkaline elution assay.
Cytotoxicity:

Cytotoxicity (% of control) at 10 mM phthalic anhydride:
TBDE-0: 93 %; TBDE-3: 91 %; MTT: 101 %; ATP: 84 %; K+: 84 %

Reliability : (2) valid with restrictions
24.02.2004 (224) (225)

Type : Ames test
System of testing : Salmonella typhimurium TA100, TA1535, TA98, TA1537, E. coli WP2uvrA
Test concentration : 0, 20, 39, 78, 156, 313, 625, 12502500, 5000 ug/plate dissolved in DMSO
Cycotoxic concentr. : 2500 ug/plate
Metabolic activation : with and without
Result : negative
Method : other: preincubation method according to OECD TG 471; highest doses used: cytotoxic, positive controls, solvent control (see also freetext ME)
Year : 1996
GLP : yes
Test substance : other TS: purity: 99.5 %

Method : positive controls:
without S9-mix:
2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide (Salmonella typhimurium TA100, TA98, Escherichia coli WP2uvrA, WP2uvrA/pKM101)
Sodium azide (Salmonella typhimurium TA1535)
4-Nitroquinoline-N-oxide (Salmonella typhimurium TA1538)
9-Aminoacridine (Salmonella typhimurium TA1538)
Bleomycin (Salmonella typhimurium TA102)
Pyruvic aldehyde (Salmonella typhimurium TA104)
with S9-mix
2-Aminoanthracene (for all strains)

Preparation of S9 fraction:
Male Sprague-Dawley rats were used for the preparation of liver fractions. Sodium phenobarbital and 5,6-benzoflavone were used as an inducer of the rat metabolic activation system. Sodium phenobarbital was injected intraperitoneally into the rats 4 days before killing and 1, 2 and 3 days before killing 5,6 benzoflavone was injected intraperitoneally. From these rats liver S9 fraction was prepared according to Ames et al. (1975) Methods for detecting carcinogens and mutagens in the Salmonella /mammalian microsome mutagenicity test. Mutat. Res. 31, 347-364. S9 was dispensed into freezing ampules and stored at -80° C. Once the stock S9 had been thawed, remained S9 was not reused.

Evaluation criteria:
The chemicals are considered to be mutagenic when dose-related increase in revertant colony count is observed and the number of revertant colonies per plate with the test substance is more than twice that of the negative control (solvent control) and when a reproducibility of the test result is observed.

Result : Phthalic anhydride was tested up to 5000 µg/plate. Cytotoxic effects were observed in the absence or in the presence of metabolic activator at concentrations equal or higher than 5000 or 313 µg/plate, respectively. Phthalic anhydride did not induce mutations in the bacterial mutation test, neither in the absence, nor in the presence of metabolic activator.

Positive and negative controls gave the expected values.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
23.11.2004 (226)

Type : Chromosomal aberration test
System of testing : Chinese Hamster Ovary (CHO)cells

Test concentration	:	6, 8, 10 mM in DMSO
Cycotoxic concentr.	:	see freetext Results
Metabolic activation	:	
Result	:	positive
Method	:	other: see freetext ME
Year	:	1998
GLP	:	no data
Test substance	:	other TS: no data on purity

Method : CHO cells and test compounds, e.g. phthalic anhydride were incubated at 37° C for 3 h in the presence or absence of S9. Cells were then washed, further incubated and harvested at 20 hours from the beginning of the treatment. Colcemid (0.1 µg/ml) was added 2-3 hours before chromosome aberration and cytotoxicity was tested.
Cytotoxicity was measured by cell counting in a Coulter counter.

In general, 200 cells from each point were scored for aberrations on coded slides. Gaps (achromatic lesions equal to or less than the width of a chromatid) were noted but not included in aberration totals.

- Criteria for positivity:
statistically significant increase over concurrent controls
in the percentages of cells with chromosomal aberrations at
two separate concentrations of test article, with about 50 % cytotoxicity, or a reproducible increase at one dose level.

- scoring: 200 cells with 19-23 chromosomes per point

- statistics: Fisher's exact test, with the P values adjusted for multiple comparisons against a common control by the method of Dunnett (J. Am Stat Assoc 50, 1096-1121, 1955).

Result : Phthalic anhydride (PA) caused a decrease in pH when added to culture medium and was immediately neutralized with 1N NaOH. In the range-finding experiment with PA, there was no statistically significant increase in aberrations at 10 mM with and without S-9 activation. Without S-9, cell counts were reduced to 59 % of controls at 10 mM. With S-9 there was little toxicity, and precipitate was visible at 8 and 10 mM. (no further data).

In a second experiment increase in aberrations to 18.5 % compared with a control of 3 %, at the top dose without S-9, and only a borderline, nonsignificant increase at 10 mM with S-9.
Conclusion: The positive result with PA was found at a concentration that caused visible precipitate.

The study is of limited reliability because:

Effects were observed only at the highest compound concentration which was "very toxic" (remaining cell counts 29%) and gave precipitate. Only a small, not statistically sigificant, increase in aberration was observed at a slightly lower concentration (8 mM compared to 10 mM) which showed lower cytotoxicity (remaining cell counts 54%) and no precipitate. The authors stated in the discussion: "Although the results we present here are for only two compounds, phthalic anhydride and ethion-amide, the data clearly show not only that precipitate can be present in medium yet not visible even under darkfield microscopy, but also that aberrations induced above the precipitate level can be false-positives, i.e., found with nonmutagenic, noncarcinogens."

Limited documentation e.g.
- no data on precise number of cells scored

- no data on precise number and type of aberrations detected
- no positive control included into the experiment

Control values in the phthalic anhydride experiment (3%) mentioned in the Results section of the publication were out of the control values described in the Materials and Methods section. "The control levels of aberrations for CHO cells ranged from 0.00-2.25% cells with aberrations, with a mean of 1.50%". No explanation for these increased control values in the phthalic anhydride experiment is given.

Reliability : (2) valid with restrictions
No concurrent positive control

Flag : Critical study for SIDS endpoint

28.04.2006 (227)

5.6 GENETIC TOXICITY 'IN VIVO'

5.7 CARCINOGENICITY

Species	:	rat
Sex	:	male/female
Strain	:	Fischer 344
Route of admin.	:	oral feed
Exposure period	:	105 w
Frequency of treatm.	:	daily
Post exposure period	:	no
Doses	:	7500, 15000 ppm = ca. 500, 1000 mg/kg bw/d
Result	:	negative
Control group	:	yes, concurrent no treatment
Method	:	other: see freetext ME
Year	:	1979
GLP	:	no data
Test substance	:	other TS: purity: 98.8 %

Method :

ANIMALS
Age: 6 weeks
50 males and 50 females/dose group
20 males and 20 females as controls

TEST DIET
Test diets containing phthalic anhydride were prepared fresh every 1 to 1-1/2 weeks at appropriate doses. The diets were routinely stored at 5 degree Celsius until used.
Analytical analyses indicated that when phthalic anhydride was mixed with Lab Meal at a concentration of 15,000 ppm and stored at room temperature for 2 weeks, the loss was 2.59% (372 ppm) per day.

ANIMAL MAINTENANCE
Polycarbonate cages; sterilizable lab meal ad libitum replenished at least 3 times per week; water acidified to pH=2.5 ad libitum; air in the animal room: 22-24° C, relative humidity: 45-55 %, 15 changes of room air per hour; fluorescent lighting on a 12 hour-per day cycle
TYPE AND FREQUENCY OF OBSERVATION
Each rat was weighed once per month, daily observations for sick, tumor bearing and moribund animals, twice daily checked for deaths
NECROPSY AND HISTOLOGICAL EXAMINATION:
At the end all animals were killed using CO2 inhalation and necropsied; gross and microscopic examination of:

skin, lungs and bronchi, trachea, bone marrow (femur), spleen, lymph nodes (mesenteric and submandibular), thymus, heart, salivary glands (patrotid, sublingual, and submaxillary), liver, pancreas, esophagus, stomach (glandular and nonglandular), small and large intestines, kidneys, urinary bladder, pituitary, adrenal, thyroid, parathyroid, pancreatic islets, testis, prostate, mammary gland, uterus, ovary, brain (cerebrum, and cerebellum), and all tissue masses. Peripheral blood smears were made for all animals, whenever possible

STATISTIC ANALYSIS
product-limit procedure of Kaplan and Meier
Method of Cox
Tarone's extensions of Cox methods
one-tailed Fisher exact test
Bonferrone inequality test
Cochran-Armitrage test
time-adjusted analysis
life-table methods

Result : F344 rats (50/sex/group) were fed diets contenting 7500 or 15,000 ppm phthalic anhydride for 105 weeks (approx. 500 and 1,000 mg/kg bw/day). The observation that the test compound is unstable (2.59% loss of activity per day at room temperature) has to be noted, although this is of minor relevance because the diet was prepared fresh every 1 to 1-1/2 weeks and the diet was stored at 5 degree Celsius, consequently the hydrolysis is assumed to be lower than 26%.

Survival and non-carcinogenic effects see robust summary chapter repeated dose toxicity.

Animal disposition summary

	Control	low-dose	high dose
Animals initial in study: males (females)	20(20)	50(50)	50(50)
Natural death	3(2)	4(6)	9(2)
Moribund sacrifice	3(1)	2(2)	5(7)
Terminal sacrifice	14(17)	44(42)	36(41)

Tumor summary:

Total animals with primary tumors	19(13)	47(37)	46(36)
Total primary tumors	37(18)	101(58)	84(53)
Total animals with benign tumors	18(12)	45(27)	43(32)
Total benign tumors	28(15)	77(38)	63(44)
Total animals with malignant tumors	7(3)	20(16)	21(8)
Total malignant tumors	7(3)	24(20)	21(9)
Total animals with secondary tumors	0(0)	0(1)	3(1)
Total secondary tumors	0(0)	0(1)	3(1)
Total animals with tumors uncertain benign or malignant	2(0)	0(0)	0(0)
Total uncertain tumors			

2(0) 0(0) 0(0)
Total animals with tumors uncertain primary or metastatic
0(0) 0(0) 0(0)
Total uncertain tumors
0(0) 0(0) 0(0)

PATHOLOGICAL EXAMINATION:
By inspection, there appeared to be no difference between the dosed and control groups in frequency or distribution of neoplasms, except for malignant lymphoma in the female rats. The incidence of malignant lymphoma in the control females was 1/20 (5%) in low-dose females, 11/50 (22%), and in high-dose females, 4/50 (8%). Due to the high and fluctuating incidence of this type of malignant lymphoma in control F344 rats, the apparent differences incidences of the tumor in the dosed and control groups were not considered to be compound related. Statistical analysis revealed that a departure from linear trend (P = 0.019) is found in the incidence of lymphoma in female rats, due to the relatively large proportion of 11/50 (22%) in the low-dose group compared with 4/50 (8%) in the high-dose group and 1/20 (5%) in the control group. The results of the Fisher exact test are not significant.
Current historical records at this laboratory indicate an incidence of lymphoma in female rats of 14/285 (4.9%), and, although the majority of the control groups had incidences of less than 5%, one control group was observed to have an incidence as high as 4/20 (20%). Since the results of the Fisher exact test were not significant and since the historical data concerning lymphoma indicates the possibility of an occasional high spontaneous rate of lymphoma, the evidence of association of the lymphomas in the dosed group of female rats with the chemical is questionable.

Further statistical analysis:
In female rats, the result of the Cochran-Armi tage test positive dose-related trend in the incidence of alveolar/ bronchiolar adenomas is significant (P = 0.020), but the results of the Fisher exact test are not significant. The results of the statistical tests on the incidences of alveolar/bronchiolar carcinomas and of alveolar/bronchiolar adenomas or carcinomas are not significant. In male rats, the results of the statistical tests on the incidences of lung tumors are not significant.

A significant dose-related trend (P = 0.037) in the negative direction is observed in the incidence of pheochromocytomas of the adrenal in male rats.

Incidence of primary tumors (%) in selected tissues:

Organ control low-dose high-dose

Male rats

Lung: Alveolar/Bronchiolar Adenoma
1/20 (5%) 4/50 (8%) 1/50 (2%)
Hematopoietic System: Lymphomas
4/20 (20%) 11/50 (22%) 12/50 (24%)
Hematopoietic System: Lymphomas or Leukemias
5/20 (25%) 12/50 (24%) 15/50 (30%) Adrenal: Pheochromocytoma
6/20 (30%) 8/48 (17%) 5/49 (10%)

Female rats

Lung: Alveolar/Bronchiolar Adenoma 0/20 (0%) 0/50 (0%) 5/50 (10%)
Carcinoma 1/20 (5%) 3/50 (6%) 1/50 (2%)
Carcinoma or Adenoma
1/20 (5%) 3/50 (6%) 6/50 (12%)
Hematopoietic System: Lymphomas
1/20 (5%) 11/50 (22%) 4/50 (8%)
Adrenal: Pheochromocytoma
0/20 (0%) 0/49 (0%) 3/49 (6%)

Severe chronic inflammatory, degenerative, or proliferative lesions frequently seen in aged rats occurred with approximately equal frequency and severity in the dosed and control groups of animals.

Conclusion: No tumors occurred in the rats of either sex at incidences that could be clearly related to the administration of the test compound. It is concluded that under the conditions of this bioassay, phthalic anhydride was not carcinogenic for F344 rats of either sex.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
24.11.2004 (214) (215) (213)

Species : mouse
Sex : male/female
Strain : B6C3F1
Route of admin. : oral feed
Exposure period : 32 w, thereafter 72 w with lower doses
Frequency of treatm. : daily
Post exposure period : no
Doses :
Result : negative
Control group : yes, concurrent no treatment
Method : other: see freetext ME
Year : 1979
GLP : no data
Test substance : other TS: purity: 98.8 %

Method : ANIMALS
age: 6 weeks
50 males and 50 females/dosegroup
20 males and 20 females as controls

TEST DIET
Test diets containing phthalic anhydride were prepared fresh every 1 to 1-1/2 weeks at appropriate doses. The diets were routinely stored at 5 degree Celsius until used.
Analytical analyses indicated that when phthalic anhydride was mixed with Lab Meal at a concentration of 15,000 ppm and stored at room temperature for 2 weeks, the loss was 2.59% (372 ppm) per day.

DOSING:
Animals were exposed via the diet at levels of 0, 25000, or 50000 ppm for the first 32 weeks of a 104 week treatment period (approx. 3570 or 7140 mg/kg bw/day). Because of excessive bodyweight loss the exposure levels in males were reduced to 12500 or 25000 ppm (approx. 1785 or 3570 mg/kg bw/day), respectively, and the doses for the females were reduced to 6250 and 12500 ppm (approx. 890 or 1780 mg/kg bw/day), respectively, for the remainder of the study. The time-weighted average doses for the males were either 16346 or 32692 ppm (approx. 2340 or 4670 mg/kg

bw/day), and those for the females were either 12019 or 24038 ppm (approx. 1717 or 3430 mg/kg bw/day).
TYPE AND FREQUENCY OF OBSERVATION
Each mouse was weighed once per month, daily observations for sick, tumor bearing and moribund animals, twice daily checked for deaths
NECROPSY AND HISTOLOGICAL EXAMINATION:
At the end all animals were killed using CO2 inhalation and necropsied; gross and microscopic examination of:
skin, lungs and bronchi, trachea, bone marrow (femur), spleen, lymph nodes (mesenteric and submandibular), thymus, heart, salivary glands (parotid, sublingual, and submaxillary), liver, pancreas, esophagus, stomach (glandular and nonglandular), small and large intestines, kidneys, urinary bladder pituitary, adrenal, thyroid, parathyroid, pancreatic islets, testis, prostrate, mammary gland, uterus, ovary, brain (cerebrum, and cerebellum), and all tissue masses. Peripheral blood smears were made for all animals, whenever possible
STATISTIC ANALYSIS
product-limit procedure of Kaplan and Meier
Method of Cox
Tarone's extensions of Cox methods
one-tailed Fisher exact test
Bonferrone inequality test
Cochran-Armitrage test
time-adjusted analysis
life-table methods

Remark : Reduction of dose because of excessive depressions in the amount of body weight gained

Result : The observation that the test compound is unstable (2.59% loss of activity per day at room temperature) has to be noted, although this is of minor relevance because the diet was prepared freshly every 1 to 1-1/2 weeks and the diet was stored at 5 degree Celsius, consequently the hydrolysis is assumed to be lower than 26%.

Body weight and Clinical Signs:
Mean body weights of dosed male and female mice were lower than those of corresponding controls throughout the bioassay, and depressions in the amount of body weight gains were dose related. In male mice, 47/50 (94%) of the high-dose group, 37/50 (74%) of the low-dose group, and 17/20 (85%) of the control group survived to the end of the bioassay. In females, 40/50 (80%) of the high-dose group, 45/50 (90%) of the low-dose group, and 16/20 (80%) of the control group survived to the end of the bioassay.

Survival and non-carcinogenic effects see robust summary chapter repeated dose toxicity.

Animal disposition summary

Control	low-dose	high dose
Animals initial in study, males (females)		
20(20)	50(50)	50(50)
Natural death		
3(4)	7(4)	2(8)
Moribund sacrifice		
0(0)	0(0)	0(0)
Accidentally killed		
0(0)	6(0)	0(1)
Terminal sacrifice		
17(16)	37(45)	41(40)
Animals missing		1(1)

Tumor summary:

Total animals with primary tumors
11(10) 21(20) 18(17)
Total primary tumors
13(11) 26(24) 21(19)
Total animals with benign tumors
2(3) 6(4) 5(3)
Total benign tumors
2(3) 6(5) 6(3)
Total animals with malignant tumors
10(7) 16(16) 15(14)
Total malignant tumors
11(8) 20(18) 15(15)
Total animals with secondary tumors
1(0) 1(0) 0(1)
Total secondary tumors
1(0) 1(0) 0(1)
Total animals with tumors uncertain
benign or malignant
0(0) 0(1) 0(1)
Total uncertain tumors
0(0) 0(0) 0(0)
Total animals with tumors uncertain
primary or metastatic
0(0) 0(0) 0(0)
Total uncertain tumors
0(0) 0(0) 0(0)

Several chronic inflammatory, degenerative, or proliferative lesions frequently seen in aged laboratory mice occurred with approximately equal frequency and severity in the dosed and control groups of animals.
The results of the Cochran-Armitage test for positive dose- related trend in incidences of tumors and those of the Fisher exact test comparing the incidence of tumors in the control group with that in each dosed group in the positive direction are not significant in either sex.

In male mice negative results are observed in the incidence of alveolar/bronchiolar carcinomas. A significant dose-related trend in the negative direction (P = 0.025) is also observed in the incidence of adenomas of the thyroid in the female mice.

Incidence of primary tumors (%) in selected tissues:

Organ
control low-dose high-dose

Male mice

Lung: Alveolar/Bronchiolar
Carcinoma
6/20 (30%) 2/50 (4%) 6/49 (12%)
Adenoma
7/20 (35%) 6/50 (12%) 9/49 (18%)

Female mice

Lung: Alveolar/Bronchiolar
Carcinoma
1/20 (5%) 3/49 (6%) 1/48 (2%)

Adenoma
1/20 (5%) 6/49 (12%) 2/48 (4%)
Thyroid:
Adenoma
2/19 (11%) 0/48 (0%) 0/46 (0%)

Based on the histopathologic examinations, the nature, incidence, or severity of the lesions observed provided no clear evidence of carcinogenic effect of the phthalic anhydride on B6C3F1 mice under the conditions of this bioassay.

Conclusion: No tumors occurred in the mice of either sex at incidences that could be clearly related to the administration of the test compound. It is concluded that under the conditions of this bioassay, phthalic anhydride was not carcinogenic for B6C3F1 mice of either sex.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
29.11.2004 (214) (215) (213)

Species : other: Syrian Hamster embryo (SHE) cell transformation assay
Sex :
Strain : other: Syrian Hamster embryo cells
Route of admin. :
Exposure period :
Frequency of treatm. :
Post exposure period :
Doses : 24 hours: control, 50, 100, 200, 300, 400 ug/ml DMSO;
Result : negative
Control group : yes
Method : other: see freetext ME
Year : 1996
GLP : no data
Test substance : other TS: purity > 99 %

Method : Cell isolation:
Pregnant Syrian golden hamsters were killed and both uterine horns were removed. After trypsination of the tissue the Syrian golden hamster embrionic cells (SHE) were cryopreserved.

Transformation assay:
SHE cells (> 100 colonies) were incubated at pH 6.7 for 7 days in the presence of the test compound (7 day-treatment) or 24 hours in the presence of the test compound, followed by a 6 day incubation in the absence of the test compound (24 h-treatment).
Cells were fixed and stained with Giemsa. Each culture was examined with a stereo microscope and the colonies were counted. Each colony was evaluated and scored to be either normal or morphologically transformed (MT). Normal colonies contain cells in a monolayer with an organized, often flowing, pattern of growth with minimal cell stacking, particularly where the cells are at a confluent density. Morphologically transformed colonies contain cells in an extensive random-oriented, three-dimensional, stacked growth pattern, with criss-crossing cells at the perimeter and in the center of the colony.

Controls:
Benzo[a]pyrene as positive control
Solvent control as negative control

An assay was considered valid if the positive control caused a statistically significant increase in transformation frequency.

Evaluation:
Total colony number
Number of morphological transformed cells/total colonies, (relative plating efficiency (RPE) in %).

Criteria for treatment related effects:
a transformation response was considered treatment related if at least 2 concentrations of phthalic anhydride caused a statistically significant increase in MT frequency relative to concurrent solvent controls.

Result : Phthalic anhydride did not show transformation activity neither after 24 h incubation nor after 7 days incubation.

24 hours	RPE(%)	MTF
Control	100	0.28
50 (µg/ml)	98	0.28
100	95	0.31
200	85	0.44
300	60	0.52
400	48	0.38

7 days		
Control	100	0.35
25	100	0.26
50	108	0.32
75	92	0.28
100	98	0.44
125	79	0.44
150	79	0.53
175	65	0.91
200	57	0.70

(Benzo[a]pyrene; positive control data from two or more trials)
1.25-10 105-95 1.22-1.66

Reliability : (4) not assignable
Positive controls were pooled from several experiments, experimental study design, no historical data. No generally accepted, valid method.

14.01.2005 (228)

5.8.1 TOXICITY TO FERTILITY

Type : other
Species : rat
Sex : male/female
Strain : Fischer 344
Route of admin. : oral feed
Exposure period : 105 w
Frequency of treatm. : daily
Premating exposure period
Male :
Female :
Duration of test :
No. of generation studies :
Doses : 7500, 15000 ppm = ca. 500, 1000 mg/kg bw/d
Control group : yes, concurrent no treatment
Method : other: see freetext ME
Year : 1979

GLP : no data
Test substance : other TS: purity: 98.8 %

Method : ANIMALS
Age: 6 weeks
50 males and 50 females/dose group
20 males and 20 females as controls

TYPE AND FREQUENCY OF OBSERVATION
Each rat was weighed once per month, daily observations for sick, tumor bearing and moribund animals, twice daily checked for deaths

NECROPSY AND HISTOLOGICAL EXAMINATION:
At the end all animals were killed using CO2 inhalation and necropsied; gross and microscopic examination of:
all major organs, including reproductive organs; in male rats preputial gland, prostate, seminal vesicle, testis and epididymis, and the mammary gland; in female rats mammary gland, uterus, endothelial gland, and ovary.

Result : SURVIVAL:
reduced from week 75 onwards in dosed male and female rats as well as in controls:
high-dose males: 36/50, and females: 41/50
low-dose males: 44/50, and females: 42/50
control males: 14/20, and females: 17/20
MEAN BODYWEIGHTS (no data given):
high dose males lower than controls
high dose females and low dose males and females comparable with controls
CLINICAL SIGNS:
dosed groups: low incidences: arched back, rough hair coat, ulceration and corneal opacity (no further details given)
PATHOLOGICAL EXAMINATION:
by inspection: no difference between the dosed and control groups

Nonneoplastic lesions on reproductive organs:

Organ	control (20)	low dose (50)	high dose (50)
Males:			
preputial gland			
cyst	0/20	1/50 (2%)	0/50
prostate			
calculus	0/20	0/48	2/45 (4%)
inflammation, suppurative	0/20	2/48 (4%)	1/45 (2%)
abscess	0/20	0/48	1/45 (2%)
Inflammation, chronic	1/20 (5%)	0/48	0/45
inflammation, chronic suppurative	1/20 (5%)	0/48	0/45
fibrosis	0	1/48 (2%)	0/45
hyperblasia, focal	1/20 (5%)	0/48	0/45
seminal vesicle inflammation, suppurative	1/20 (5%)	0/50	0/50
testis			
hemorrhage	0/20	0/50	1/50 (2%)
infarct	0/20	1/50 (2%)	0/50
atrophy	0/20	3/50 (6%)	2/50 (4%)
epididymis inflammation, chronic			

	0/20	0/50	1/50 (2%)
mammary gland dilatation/ducts	5/20 (25%)	12/50 (24%)	12/50 (24%)

Females:

mammary gland	20	50	50
dilatation/ducts	13 (65%)	33 (66%)	24 (48%)
galactccele	1 (5%)	4 (8%)	1 (2%)
inflammation, granulomatous	0	1 (2%)	0
fibrosis	0	0	1 (2%)
hyperplasia, Nos	0	0	1 (2%)
hyperplasia, focal	1 (5%)	0	0
hyperplasia, cystic	0	0	1 (2%)
uterus	19	47	50
hematoma	0	0	1 (2%)
dilatation, nos	0	1 (2%)	0
necrosis, nos	1 (5%)	0	0
uterus/endometrium	19	47	50
dilatation, nos	0	1 (2%)	1 (2%)
cysti, nos	0	1 (2%)	0
hyperplasia, epithelial		1 (2%)	0
endothelial gland	19	47	50
dilatation, nos	3 (16%)	0	0
ovary	19	47	50
cyst, nos	1 (5%)	3 (6%)	1 (2%)
inflamation, chronic	1 (5%)	0	0
hypoplasia, nos	0	1 (2%)	0

NOAEL: 15000 ppm.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
24.11.2004 (214) (215) (213)

Type :
Species : rat
Sex : male
Strain : other: white
Route of admin. : inhalation
Exposure period : 45 w, 24 hours a day
Frequency of treatm. : daily
Premating exposure period
Male :
Female :
Duration of test :
No. of generation studies :
Doses :
Control group : yes, concurrent no treatment
Method : other: see freetext ME
Year : 1970
GLP : no
Test substance : other TS: no data on purity

Method : Groups of 6 male rats were exposed to 0, 0.02, 0.2, 1 mg/m3 phthalic anhydride for 45 days, 24 hours/day. Testes were dissected in the recovery

phase, two weeks after the end of dosing.
The amount of ascorbic acid, dehydroascorbic acid, RNA and DNA were investigated in the testes.
Sperm mobility was investigated with a light-microscope.

Result : The amount of ascorbic acid and dehydroascorbic acid in the testes decreased in the testes, and the amount of RNA increased in the testes.

	Control	0.02	0.2	1 mg/m3
Ascorbic acid (mg%)	31,25±1,36	29,51±0.86	24,70±0,57	19,19±0,48
Dehydroascorbic acid	2,39±0,11	1,90±0,13	140±0,14	0,29±0,05
RNA (mg%)	1,5±0,32	1,78±0,24	1,72±0,25	2,43±0,25

Sperm mobility:

Control: 82 minutes (no further data, no SD given)
0.02 mg/m3: no data
0.2 mg/m3: 60 minutes (no further data, no SD given)
1 mg/m3: 40 minutes (no further data, no SD given)

Reliability : (4) not assignable
Poor documentation, no data on variability of the test systems; no data on historical data, no data on biological and statistical relevance of the observed effects, no data on test atmosphere, no data on other endpoints

Flag : Critical study for SIDS endpoint
24.11.2004 (229)

Type :
Species : mouse
Sex : male/female
Strain : B6C3F1
Route of admin. : oral feed
Exposure period : 32 w, thereafter 72 w with lower doses
Frequency of treatm. : daily
Premating exposure period
Male :
Female :
Duration of test :
No. of generation studies :
Doses :
Control group : yes, concurrent no treatment
Result : negative
Method : other: see freetext ME
Year : 1979
GLP : no data
Test substance : other TS: purity: 98.8 %

Method : ANIMALS
age: 6 weeks
50 males and 50 females/dose group
20 males and 20 females as controls
TIME HELD BEFORE STUDY:
2 weeks

DOSING:
Animals were exposed via the diet at levels of 0, 25000, or 50000 ppm for the first 32 weeks of a 104 week treatment period (approx. 3570 or 7140 mg/kg bw/day). Because of excessive bodyweight loss the exposure levels

in males were reduced to 12500 or 25000 ppm (approx. 1785 or 3570 mg/kg bw/day), respectively, and the doses for the females were reduced to 6250 and 12500 ppm (approx. 890 or 1780 mg/kg bw/day), respectively, for the remainder of the study. The time-weighted average doses for the males were either 16346 or 32692 ppm (approx. 2340 or 4670 mg/kg bw/day), and those for the females were either 12019 or 24038 ppm (approx. 1717 or 3430 mg/kg bw/day).

TYPE AND FREQUENCY OF OBSERVATION
Each mouse was weighed once per month, daily observations for sick, tumor bearing and moribund animals, twice daily checked for deaths

NECROPSY AND HISTOLOGICAL EXAMINATION:
At the end all animals were killed using CO2 inhalation and necropsied; gross and microscopic examination of all major organs, including reproductive organs.

Remark : Reduction of dose because of excessive depressions in the amount of body weight gained

Result : SURVIVAL:
reduced from week 90 onwards in dosed male and female rats as well as in controls:
high-dose males: 47/50, and females: 40/50
low-dose males: 37/50, and females: 45/50
control males: 17/20, and females: 16/20
MEAN BODYWEIGHTS (no data given):
because of excessive depressions in the amount of body weight gained
reduction of dose from week 72 onwards
PATHOLOGIC EXAMINATION:
no findings that could be attributed to treatment
in male mice epididymis; in female mice uterus and ovary.

Male mice:

	Matched	low dose	high dose control
Reproductive System			
Epidymis	20	50	49
inflamation, chronic	1 (5%)	0	0

Female mice:

	Matched	low dose	high dose control
reproductive system			
uterus	19	48	46
dilatation, nos	2 (11%)	0	0
edema, nos	0	1 (2%)	0
pycmetra	0	0	1 (2%)
uterus/endometrium	19	48	46
dilatation, nos	5 (26%)	29 (60%)	20 (43%)
inflammation, nos	0	1 (2%)	0
inflammation, chronic	0	1 (2%)	0
hyperplasia, papillary	0	0	1 (2%)
hyperplasia, cystic	0	0	1 (2%)
ovary	18	48	47
cyst, nos	2 (11%)	26 (54%)	7 (15%)
hemorrhagic cyst	1 (6%)	1 (2%)	1 (2%)

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
23.03.2004 (214) (215) (213)

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	rat
Sex	:	
Strain	:	Wistar
Route of admin.	:	oral feed
Exposure period	:	GD 7-16
Frequency of treatm.	:	daily
Duration of test	:	10 days
Doses	:	0, 1.25, 2.5, 5% (approx. 0, 1000, 1700, 3000 mg/kg bw/day)
Control group	:	yes
NOAEL maternal tox.	:	= 1000 mg/kg bw
NOAEL teratogen.	:	= 1700 ml/kg bw
Method	:	other: see freetext ME
Year	:	1997
GLP	:	no data
Test substance	:	other TS: phthalic acid, purity 99.5%

Method :

Pregnant rats were fed a diet containing phthalic acid (99.5% pure).The administration in the feed was selected because of the necessity to expose to large amount of phthalic acid and slight solubility of phthalic acid in water and oil. This method for administration is useful with agents that are to be given in large amounts or are difficult to dissolve in vehicles that would be tolerated in other treatment routes. The diet containing phthalic acid was freshly prepared every week. A pre-determined amount of phthalic acid was weighed and added to a small aliquot of ground basal diet and handblended. This premix was then added to a preweighed ground basal diet and blended with mill for 30 min. The control rats were fed a basal diet only ad libitum.

Virgin female Wistar rats, about 12 weeks old, were mated overnight with male rats. The pregnant rats were distributed on a random basis into four groups of 11 pregnant rats each and housed individually.
The pregnant rats were fed a diet containing phthalic acid at a dose of 0, 1.25, 2.5, or 5.0% ad libitum on GD 7 - GD 16.

The pregnant rats were observed daily for evidence of clinical signs of toxicity. Maternal body weight and food consumption were recorded daily. Average daily intake of phthalic acid was calculated. The pregnant rats were sacrificed on day 20 of pregnancy. The peritoneal cavity and uterus were opened and the numbers of live and dead fetuses and resorptions were counted. The gravid uterus was removed and the rats weighed again. The adjusted weight gain, i.e. maternal weight gain throughout pregnancy corrected for gravid uterine weight, was calculated. The live fetuses removed from the uterus were sexed, weighed and inspected for external malformations and malformations within the oral cavity. Approximately two-thirds of live fetuses in each litter, randomly selected, were fixed in 99% ethanol, stained alizarin red S and examined for skeletal malformations. The remaining live fetuses in each litter were fixed in Bouin's solution and examined for internal malformations.

Result : Maternal toxicity occurred in the 2.5 and 5.0% groups as can be seen by significant decreases in the maternal body weight gain and food consumption during the administration period. No significant changes in maternal parameters were found in the 1.25% group. Neither deaths nor clinical signs of toxicity were noted in any groups. No significant changes induced by phthalic acid were detected in the incidence of postimplantation loss and number and sex ratio of live fetuses. Significant decreases in the

weight of male fetuses and number of ossification center of the caudal vertebrae were found in the 5.0% group. Morphological examinations of fetuses revealed no evidence of teratogenesis.

Dose group (%):	O	1.25	2.5	5.0
Maternal findings:				
No. of pregnant rats:	11	11	11	11
No. of dead pregnant rats:	0	0	0	0
Initial body weight(g):	242	243	243	244
Body weight gain during pregnancy (g):				
Days 0-7:	24	26	31	27
Days 7-16:	49	54	40*	20**
Days 16-20:	41	40	47	57**
maternal weight gain excluding the gravid uterus:	50	47	42	30**
Food consumption during pregnancy:				
Days 0-7:	138	140	145	138
Days 7-16:	198	197	173**	145**
Days 16-20	88	98**	101**	120**

Daily intake of phthalic acid (mg/kg):

0	1021	1763	2981

Reproductive findings:				
No. of litters	11	11	11	11
No. of corpora lutea per Utter:	14.3	15.3	15.7	15.7
No. of implantations per litter	13.1	14.0	14.3	13.8
No. of litters totally resorbed	0	0	0	0
No. of resorptions and dead fetuses per litter	1.6	1.3	0.9	1.3
% postimplantation loss per litter	14.2	9.3	5.8	8.7
No. of live fetuses per litter	11.5	12.7	13.4	12.5
Sex ratio of live fetuses (male/female)	60/66	61/79	83/64	62/76
Body weight of live fetuses (g)				
Male	4.19	4.15	4.20	4.03*
Female	3.92	3.95	3.92	3.82

Morphological findings in fetusses:				
External examination				
No. of fetuses(litters) examined:	126(11)	140(11)	147(11)	138(11)
No. of fetuses(litters) with malformations:	0	0	0	0
Skeletal examination				
No. of fetuses(litters) examined:	84(11)	94(11)	97(11)	92(11)
No. of fetuses(litters) with malformations:	0	0	0	0
No. of fetuses(litters) with variations:	4(3)	5(4)	4(3)	10(6)
No. of fetuses(litters) with:				
Splitting of thoracic				

vertebral bodies: 1(1) 0 0 0
Asymmetry of stemebrae:
3(3) 4(3) 4(3) 7(6)
Splitting of sternebrae:
0 1(1) 0 5(3)
Degree of ossification
No. of ossification centers
of caudal vertebraea: 5.5 5.3 5.4 5.1*
No. of stemebrae 5.9 6.0 6.0 5.9

Intemal examination
No. of fetuses(litters)
examined: 42(11) 46(11) 50(11) 46(11)
No. of fetuses(litters)
with malformations: 0 0 0 0

*, ** Significantly different from the control, P<0.05 and P<0.01, respectively.

Reliability : (2) valid with restrictions
No GLP, small number of dams, good documentation
Flag : Critical study for SIDS endpoint
02.03.2006 (230)

Species : mouse
Sex : female
Strain : CD-1
Route of admin. : i.p.
Exposure period : 3 d
Frequency of treatm. : 8.-10. d of pregnancy
Duration of test :
Doses : highest dose: 0.19 mmol/kg bw/day, as suspension in 0.5% carboxymethylcellulose
Control group : yes, concurrent vehicle
Method :
Year : 1982
GLP : no
Test substance : other TS: purity: > 98 %

Method : Animal maintenance:
housing in climate-controlled conditions: 20° C, 50 % humidity, free access to water and feed

1) Adult lethality testing:
administration of the compound to female nonpregnant mice (n=10) on 3 consecutive days as single daily intraperitoneal injections: a geometric progression of at least 5 doses was used. Deaths were recorded for up to 14 days after final injection. LD01 and LD50 values were reported. Dosing was started at the 95% confidence limit of the LD01 and progressing geometrically downward until no effect was observed; dose and number of dose groups not indicated.

2) Teratogenicity testing:
Dams were treated daily with intraperitoneal injections on pregnancy days 8-10.
4 or more dose levels with at least 10 dams per group were used.
Vehicle controls were included.
Sacrifice of the mice on day 18, removal of the uteri and determination of numbers and location of live, dead, and resorbing conceptuses.
All live fetuses were examined gross- and histo-pathologically, developmental aberrations were recorded. All developmental aberrations

were recorded, but for the purpose of this study, some minor defects were not classified as malformations. These included: undescended testes, extra lung lobe, and several minor skeletal variants (cervical ribs, extra thoracic vertebra with pair of ribs).

3) Analysis of data:
The dose-response trends of adult lethality and fetal malformations were examined by computerized probit analysis. Frequency of fetal malformation at each dose level was taken as the total number malformed/total number of live fetuses, and a constant background rate of malformations of 1.08 % was included in the analysis. Results were expressed as doses required to induce an additional 5 or 50% malformation rate above background (tD05 and tD 50, respectively).

Result : No details of the teratogenic effects of phthalic anhydride were reported.

Maternal lethality
LD01 0.37 mmol/kg bw/day (54.8 mg/kg bw/day), confidence limit: (0.19-0.43)
LD50 0.51 mmol/kg bw/day (75.5 mg/kg bw/day), confidence limit: (0.44-0.57))

Teratogenicity
tD05 0.40 mmol/kg bw/day (59.2 mg/kg bw/day), confidence limit: (could not be calculated by the computer program)
tD50 1.37 mmol/kg bw/day (202.8 mg/kg bw/day), confidence limit: (could not be calculated by the computer program)

Reliability : (4) not assignable
The study is of limited reliability because of the study design and the poor documentation.

Study design:
I.p. administration is not a relevant administration route to investigate developmental toxicity in particular if the compound is an irritant. Observed effects might be related to irritation at the site of dosing. Additionally, phthalic anhydride is known to undergo rapid hydrolysis to phthalic acid on contact with water and it is likely that a similar reaction will occur in biological systems. Consequently, the parent compound, phthalic anhydride, will not reach the reproductive organs.

Maternal toxicity was investigated in female non-pregnant mice (n=10) dosed on 3 consecutive days; a geometric progression of at least 5 doses was used. The only parameter investigated was lethality, and recorded for up to 14 days after final injection. LD01 and LD50 values (extrapolations) were reported. It is unclear whether the extrapolation from non-pregnant to pregnant mice is actually justified.

Documentation:
No data on precise doses and number of dose groups .
No data on positive and negative controls.
No primary data on the phthalic anhydride experiment given in the publication. LD01, LD50, tD05, and TD50 values are extrapolated without any information on measerred figures.

No 95% confidence limits could be calculated for teratogenicity of phthalic anhydride, probably because of a "very shallow dose-response curve". Consequently, the biological relevance of the data presented is questionable, because of the lack of information on the biological variability in this test (no negative control values given); the dose-response curves might be statistically correct but without any biological relevance

Flag : Critical study for SIDS endpoint

06.03.2006 (231)

Species	:	mouse
Sex	:	female
Strain	:	CD-1
Route of admin.	:	i.p.
Exposure period	:	3 days
Frequency of treatm.	:	gd 8-10 or gd 11-13
Duration of test	:	no data
Doses	:	80 mg/kg bw/day
Control group	:	no data specified
Method	:	
Year	:	1978
GLP	:	no
Test substance	:	other TS: no data on purity given
Method	:	Pregnant CD-1 mice (number not given) were dosed with phthalic anhydride by the i.p. route on three consecutive days. a) GD 8-10 80 mg/kg bw/day b) GD 11-13 no data given
Result	:	a) 14.4 % or 11,5 % of the viable offspring were malformed. Branched ribs, fused vertebrae and cleft palatewere the most common defects. b) Phthalic anhydride was significantly teratogenic; no further data.
Reliability	:	(3) invalid Insufficient information, abstracts only; i.p. application is an exposure route of unknown relevance for the human situation.

02.03.2006 (130) (232) (131)

Species	:	mouse
Sex	:	female
Strain	:	CD-1
Route of admin.	:	i.p.
Exposure period	:	3 d
Frequency of treatm.	:	gd 8-10 or gd 11-13
Duration of test	:	
Doses	:	0.375 mmol/kg = 55.5 mg/kg bw/d
Control group	:	no data specified
Method	:	
Year	:	1978
GLP	:	no
Test substance	:	other TS: no data on purity given
Method	:	Teratogenicity was evaluated following i.p. administration of TS to pregnant CD-1 mice on gd 8-10 or 11-13 (no further information)
Result	:	Phthalic anhydride caused fetal abnormalities, with both dose schedules. The minimal dose of phthalic anhydride to produce significant increase in defects for treatment days 11-13 was 0.375 mmol/kg bw/d.
Reliability	:	(3) invalid Insufficient information, abstract only; i.p. application is an exposure route of unknown relevance for the human situation.

02.03.2006 (233)

Species	:	other: chicken embryo
Sex	:	
Strain	:	other: white Leghorn
Route of admin.	:	other
Exposure period	:	11 d
Frequency of treatm.	:	1 injection on day 3
Duration of test	:	
Doses	:	1.4, 0.68, 0.34, 0.17 µmol/egg = 207, 101, 50, 25 µg/egg

Control group : yes, concurrent vehicle
Method :
Year : 1983
GLP :
Test substance : other TS: purity: technical grade

Method : White Leghorn chicken eggs with three day embryos were selected by candling. The test compound or the solvent (acetone) was injected into the egg in the total volume of 5 µl. Eggs were incubated for 14 days.
The affected embryos were classified into the following categories:
1. Early deaths, embryos, that died before day 5 of the incubation, within two days of the treatment.
2. Late deaths, non-malformed, externally normal embryos that died between days 5 to 14.
3. Late deaths, malformed, externally malformed embryos that died between days 5 to 14.
4. Malformed survivors, externally malformed embryos alive on day 14 of the incubation.

LD50 and ED50 values were calculated.

Result :

Dose (µmol/egg)	Early deaths	Late deaths	Malformed embryos	All affected
1.4	20/20	0	0	20/20
0.68	19/30	0	6	25/30
0.34	6/30	0	5	12/30
0.17	0/30	0	3	3/30
acetone-control	8/260		9/260	

total ED50 for embryotoxicity: 0.38 µmol/egg (corresponds to 56 µg/egg)

Reliability : (4) not assignable
Testsystem not validated to investigate teratogenic effects in mammals.

24.11.2004 (234)

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

Remark : For humans, phthalic anhydride in the form of vapor, fume or dust is a primary irritant to mucous membranes and the upper respiratory tract. Initial exposure produces coughing, sneezing, burning sensations in the nose and throat, and increased mucous secretion. Repeated or continued exposures may result in general inflammation of the respiratory tract, nasal ulceration and bleeding, atrophy of the mucous membranes (reversible), loss of smell, hoarseness, bronchitis, urticaria, blood changes and symptoms of allergic hypersensitivity.
It is questionable if phthalic anhydride causes meat-wrapper's asthma as was claimed.

07.04.2004 (235) (236) (237) (238) (239) (240) (241) (203) (242) (243) (206) (244) (245) (246) (247) (248) (249)

Remark : Mortality from lung cancer in an acetylene and phthalic anhydride plant: a case-referent study. The study tested the hypothesis that an excess of lung cancer observed in a chemical plant which is producing mainly acetylene, phthalic anhydride, and their derivatives was attributable to occupational exposures. Exposures included a large number of chemicals, some of which are known or suspected carcinogens such as soot and phthalates. The local register of deaths was the source of the cases and referents. The cases (n=43) were the male residents in the town who had died from lung cancer from 1976 to 1979. The referents were a sample of residents from the same town who had died during the same four-year period from causes other than respiratory cancer. Causes of death were validated through clinical data and relatives' reports. Information for a complete occupational history and on smoking habits was collected in interviews of the next of kin of each study subject. After control for age and smoking, the risk of dying from lung cancer for the subjects previously employed at the chemical plant relative to those never occupationally exposed was 5.6 (95 % confidence limits 1.9-16.2). The risk for exposure to lung carcinogens in work environments other than in the plant was 1.7 (95 % confidence limits 0.9-3.5). On the whole, occupational exposure to chemical carcinogens accounted for about one-third of the total number of lung cancer deaths that occured in the area during the study period.

Reliability : (4) not assignable
Mixed exposure, no data on exposure

25.02.2004 (250)

Remark : Sensitized people can have serological reactivity to phthalic anhydride, both IgE and IgG, but IgE appears to discriminate cases of asthma from workers without asthma better than IgG, because the prevalence of IgG is high in exposed workers

22.03.2004 (251) (252) (253) (254) (193) (255) (166) (195) (172) (202) (175) (205) (256) (257) (258) (132) (249)

Remark : Prompt healing of corneal burn was reported in 8 individuals within 48 h after phthalic anhydride exposure by an ophthalmologist.

(259)

Remark : The occupational exposure to phthalic anhydride from 1955 to 1967 resulted in asthmoid bronchitis in three employees. Some of the empolyees suffered from signs of irritation in skin and eyes

Source : BASF AG Ludwigshafen

(260)

Remark : A man developed asthma after grinding epoxy resin moulds made from bisphenol A, with phthalic anhydride as a hardener. He was shown to have a dual asthmatic response after inhalation of phthalic anhydride fumes. It is postulated that his asthma was caused by the release of phthalic anhydride during the grinding of cured moldings

19.03.2004 (261)

Remark : During 1977-1993 some 200 personnel were exposed to phthalic anhydride in connection with its manufacture at one plant. Measured exposure levels were up to 5 mg/m3 (long term, 3.5 hours) and 20 mg/m3 (short term, 1.5 minutes). Medical records showed that in the period just seven employees reported with symptoms to the same medical practitioner. The autors

stated that there was no evidence that symptoms were due to sensitisation but could have been due to irritating effects.

Source : BP chemicals Ltd.

(262)

Type of experience : other: occupational exposure

19.03.2004 (263) (264) (265) (266) (267) (268) (269)

Type of experience : other: case report

Remark : Case of a 38-year-old female tanker driver suffering from Reactive Airway Disease Syndrome (RADS)
Patient accidentally inhaled a high concentration of gaseous phthalic anhydride for bout 10 min. she immediately felt a burning of the upper airways and started coughing. 3 months later she complained of wheezing, dyspnea at rest as well as chest tightness. One year later she was asymthonic.

Reliability : (2) valid with restrictions

Flag : Critical study for SIDS endpoint

19.03.2004 (270)

Remark : A case of late respiratory systemic syndrome (LRSS) caused by phthalic anhydride is reported: shortness of breath, fever, headache, arthralgia, myalgia, skin prick test positive. the patient's sensitivity to PA was confirmed by PA-bronchoprovocation test.

25.02.2004 (271)

Remark : Phthalic anhydride was detected in welding fume. In the breathing zone of the welder, the concentration ranged from 10.9 to 20.9 µg/m3 (mean 16.1 µg/m3, SD 3.8, n=5).

22.03.2004 (272)

Remark : Acute effects of phthalic anhydride in humans:
After acute intoxication to anhydride dust or vapor a feeling of suffocation, headache, dizziness, nausea and epigastric burning was described.

Reliability : (2) valid with restrictions
No information on exposure levels

Flag : Critical study for SIDS endpoint

19.03.2004 (273)

Remark : In case of blistering and ulceration of the skin following contact with phthalic anhydride, transient renal insufficient with anuria was noted in one person occasionally exposed to phthalic anhydride

Flag : Critical study for SIDS endpoint

19.03.2004 (274)

Remark : The first case of asthma and allergic rhinitis found to be due to sensitivity to phthalic anhydride. A chemist (29 years) troubled with stuffiness of the nose and a profuse watery nasal discharge. Skin tests with an extensive list of substances gave a strong positive reaction to phthalic anhydride in crystalline form. Neither the solution nor the actual crystals gave positive scratch reactions in normal controls.

Reliability : (2) valid with restrictions

Flag : Critical study for SIDS endpoint

19.03.2004 (275)

Remark : For humans, phthalic anhydride in the form of vapor, fumes, or dust is an irritant to mucous membranes and the upper respiratory tract. Initial exposure produces coughing, sneezing, burning sensations in the nose and throat, and increased mucous secretion. Repeated or continued exposures may result in general inflammation of the respiratory tract, nasal ulceration and bleeding, atrophy of the mucous membranes (reversible), loss of smell, hoarseness, bronchitis, urticaria, blood changes and symptoms of allergic hypersensitivity
Reliability : (2) valid with restrictions
No information on exposure levels
Flag : Critical study for SIDS endpoint
19.03.2004 (236) (276)

Remark : On moist skin, phthalic anhydride is hydrolyzed to phthalic acid which causes irritation; eczema has been observed occasionally also urticaria. Impurities present in the technical phthalic anhydride, naphthoquinone and maleic anhydrides, seem to contribute to these symptoms.
Reliability : (2) valid with restrictions
No information on exposure levels
Flag : Critical study for SIDS endpoint
19.03.2004 (8)

Remark : Twenty-three subjects employed on the production of phthalic anhydride were investigated.

All the workers examined belonged to the bagging department.
In this department, a previous environmental study had found values of PA of between 1.1 mg/m3 and 14.7 mg/m3.

The subjects were males and with an average age of 53.6 ± 5.9.

The subjects:
1) completed a questionnaire about their history;
2) Underwent a clinical examination
3) Underwent respiratory function tests
4) Underwent aspecific bronchial stimulation tests
5)) Specific exposure tests with phthalic anhydride:
a) Exposure to PA dust using an occupational method: a mixture of dusts of PA for 30 minutes in an inhalation cabin.
b) Exposure for 15 minutes in the same cabin to vapors of PA obtained by evaporating a quantity of pure substance sufficient to produce an atmosphere of 6 mg/m in the cabin, equal to the ACGIH TLV, and mean value with reference to the amounts of PA found in the environmental investigation.
6) Allergometric skin tests
7) 7) Detection of specific IgE

RESULTS:
Twenty-three subjects employed on the production of phthalic anhydride answered a questionnaire as to their history, and underwent a clinical examination, broncho-stimulation tests with methacholine and with an ultrasonic spray of distilled water, and specific phthalic anhydride exposure tests.

Rhinitis-type signs and symptoms were found in 12 patients, associated in

4 cases with conjunctivitis, and associated in 2 cases with real attacks of asthma. Two patients have only a dry cough on contact with phthalic anhydride.

Where the test with methacholine is concerned, there was a significant bronchial response in 5 out of 22 cases (22.7%).

As for the distilled water test, which was carried out in 21 of the 23 subjects, 3 significant bronchial responses were obtained.

There were 12 significant nasal responses (60%) out of 20 subjects after exposure to phthalic anhydride dusts; 8 (42.1%) out of 19 after exposure to vapors; considering the specific tests overall, 15 positive nasal responses out of 20 were obtained (75%). The mean percentage increase for Rn after specific exposure tests (with dusts or vapours) was 180.8 ± 254.7. Agreement with the rhinitis-type signs and symptoms was 91.6% (Table 8).

Detection of specific IgE's for phthalic anhydride was negative in all the subjects.

The authors conclude that the chemical compound under investigation has an irritative action on the respiratory tract, and on the nasal mucosa in particular.

19.03.2004 (277)

Remark : Eye irritation (conjunctivitis) and runny nose (rhinitis) were noted in a group of 25 persons exposed to phthalic anhydride dust concentrations below 0.2 mg/m3 for 0.3-40 years. Since the workers were exposed to several anhydrides (i.e., maleic anhydride, isophthalic anhydride, and trimellitic anhydride, but "to a much lower degree" than phthalic anhydride) quantitative values cannot be derived from this study.

02.03.2006 (278)

Reliability : (2) valid with restrictions

29.11.2004 (279)

Type of experience : other: Biological monitoring at the workplace

Result : Phthalic anhydride specific immunoglobin E (IgE) was detected by a radio-allergosorbent test (RAST) in the serum of a chemical worker with hypersensitivity to phthalic anhydride

Reliability : (2) valid with restrictions
Basic data given

Flag : Critical study for SIDS endpoint

21.10.2005 (175)

Type of experience : other: Biological monitoring at the workplace

Result : Severe immunoreactions were observed in 2 industrial workers exposed to phthalic anhydride dust for 3 months and for 35 years, respectively. The phthalic anhydride specific IgE levels in these 2 workers and in 2 other workers cross-sensitized with the structurally related anhydrides, hexahydro phthalic anhydride and himic anhydride, were 10 - 12-fold compared to a control group of 30 unexposed persons

Reliability : (2) valid with restrictions
Basic data given

Flag : Critical study for SIDS endpoint

21.10.2005 (252)

Type of experience : other: Biological monitoring at the workplace

Remark : Exposure data see IUCLID 3.2.1
Result : The presence of serum IgE antibodies to phthalic anhydride was demonstrated in 4 workers out of 54 exposed occupationally to phthalic anhydride dust in alkyd and/or saturated polyester resin plants
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
24.10.2005 (84)

Type of experience : other: Biological monitoring at the workplace

Result : Compared to controls, the levels of IgG specific to phthalic anhydride human serum albumin adducts were increased 4 - 6-fold in exposed workers e.g. a lab technician testing the quality of phthalic anhydride. Consistently, in exposed workers, the levels of IgE were also increased 2 - 6-fold.
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
06.03.2006 (280)

Type of experience : other: Biological monitoring at the workplace

Remark : Exposure data see IUCLID 3.2.1
Result : The levels of serum IgE antibodies to phthalic anhydride determined with RAST were similar in workers exposed to phthalic acid and in controls. However, the total IgE level in workers of 32 kilounits/liter (ku/l) was twice the level in controls (15 ku/l). Determined with an enzyme-linked immunosorbent assay (ELISA), the level of specific antibodies against phthalic anhydride antigen (IgG) were 0.21 OD in workers, to 0.12 OD in controls
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
24.10.2005 (85)

Type of experience : other: Biological monitoring at the workplace

Result : In another study, the RAST values of 3 workers exposed to phthalic anhydride were 6, 13, and 34 compared to < 0.3 in controls, indicating high antibody levels against phthalic anhydride in these workers
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint
24.10.2005 (281)

Type of experience : other: Biological monitoring at the workplace

Result : Baur et al. (1995) examined a group of 96 workers exposed to several acid anhydrides, including phthalic anhydride, in 2 German chemical plants. 9 workers with clinical allergic symptoms and 2 without clinical allergic symptoms, had IgE levels higher than 0.35 ku/l in an enzyme-allergo-sorbent test, and 48 symptomatic workers and 42 asymptomatic workers had IgE levels of less than 0.35 ku/l.
Reliability : (2) valid with restrictions
Basic data given
Flag : Critical study for SIDS endpoint

24.10.2005 (165)

Type of experience : other: Biological monitoring at the workplace

Remark : Exposure data see IUCLID 3.2.1

Result : In a US factory manufacturing phthalic anhydride, di(2-ehtylhexyl)phthalate, and other phthalates, pronounced increases of urinary phthalate concentrations occurred only in chemical operators during shift. Since the urine samples were hydrolyzed and determined as dimethylphthalate, it cannot be distinguished between the molecular species potentially present in urine, e.g. phthalic anhydride, phthalic acid, di(2-ethylhexyl)phthalate, or mono(2-ethylhexyl)phthalate. However, by additional examinations, neither di(2-ethylhexyl)phthalate, nor mono(2-ethylhexyl)phthalate could be detected in urine samples. There was no correlation between the increase in urinary phthalate concentrations and the workplace air concentrations of phthalic anhydride and/or of di(2-ethylhexyl)phthalate. The results of the biological monitoring of total phthalate in urine of three exposure groups are presented in Table 9. One of the highest post-shift phthalate concentration occurred in an administrator who was unlikely to be exposed during work. The pre-shift urinary phthalate concentration of this administrator was actually higher than his post-shift value.
Urinary phthalate concentrations in workers of a phthalic anhydride manufacturing and processing plant (in braketts ± standard deviation)
Preshift:
High exposure, with detectable airborne phthalic anhydride in personal sample: 26 participants with preshift urinary phthalate concentration (mean, µmol/l) 5.6 ± 3.4;
27 participants with postshift urinary phthalate concentration (mean, µmol/l) 9.9 ± 8.7
High exposure, without detectable airborne phthalic anhydride in personal sample: 20 participants with preshift urinary phthalate concentration (mean, µmol/l) 4.9 ± 6.1; 19 participants with postshift urinary phthalate concentration (mean, µmol/l) 6.8 ± 8.1
Control (low exposure): 41 participants with preshift urinary phthalate concentration (mean, µmol/l) 6.4 ± 6.7; 40 participants with postshift urinary phthalate concentration (mean, µmol/l) 5.9 ± 5.8

Reliability : (2) valid with restrictions
Basic data given

Flag : Critical study for SIDS endpoint

24.10.2005 (83)

5.11 ADDITIONAL REMARKS

Type : other

Remark : Review on toxicity

02.05.2003 (282) (283)

Type : other

Remark : Exposed syrian hamster embryo cells: no effect on ornithine decarboxylase

06.02.1998 (284)

Type : other

Remark : Formation of in vitro adducts between different classes of xenobiotics (including phthalic anhydride) and the lysine-containing peptide Lys-Tyr

was monitored by high-performance liquid chromatography and electrospray ionization mass spectrometry.
Result: adduct formation was observed
22.03.2004 (285)

Type : other

Remark : Chemicals with skin sensitizing potential (including phthalic anhydride) were incubated with a peptide, glutathione, and resultant mixtures were analyzed by mass spectrometry. Eighteen chemicals were assessed, and new peaks corresponding to chemical-peptide conjugates were detected by MS.
Conjugates were detected for phthalic anhydride. The authors stated that: "The method has advantages as a simple screening assay for assessing the sensitization potential of chemicals."
19.03.2004 (286)

Type : other

Remark : Cross reactivity of IgE induced by different anhydrides was reported.
Flag : Critical study for SIDS endpoint
22.03.2004 (252)

Type : other: cytotoxicity

Remark : Phthalic anhydride (0.001-1 mM) dissolved in DMSO was added to a Ascites sarcoma BP8 cell suspension and incubated for 48 hours at 37° C. The growth rate of the cells was calculated and compared to the average value of 8-10 controls performed in each series of experiments.

Result: 1 mM phthalic anhydride caused 14 % inhibition on cell culture growth rate (no further information).
Reliability : (2) valid with restrictions
No GLP
04.03.2004 (287)

Type : other: review on phthalic acid

22.03.2004 (288) (289)

Remark : The irritation caused by pure phthalic anhydride in rats and guinea pigs is enhanced by by-products like naphthoquinone and maleic acid and other compounds of unknown structure

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- Indirect Photodegradation with SRC-AOPWIN v. 1.91, 2000
- Soil Adsorption Coefficient with SRC-PCKOCWIN v. 1.66, 2000
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