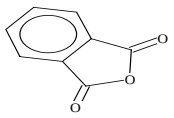
SIDS INITIAL ASSESSMENT PROFILE

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.