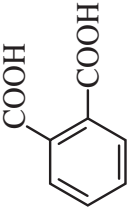
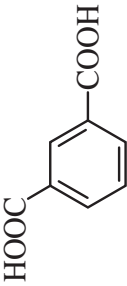
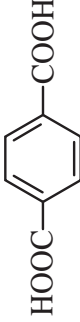


Phthalic acid and its isomers (isophthalic acid and terephthalic acid)

	phthalic acid	isophthalic acid	terephthalic acid
MAK value (2005)	not yet established; see Section IIb of the <i>List of MAK and BAT Values</i>	2 mg/m ³ I	0.1 mg/m ³ I
Peak limitation (2005)	–	Peak limitation category I, excursion factor 2 –	Peak limitation category I, excursion factor 2 –
Absorption through the skin	–	–	–
Sensitization	–	–	–
Carcinogenicity	–	–	–
Prenatal toxicity (2006)	–	Pregnancy risk group C	Pregnancy risk group C
Germ cell mutagenicity	–	–	–
BAT value	–	–	–
Synonyms	benzene-1,2-dicarboxylic acid o-benzenedicarboxylic acid o-dicarboxybenzene o-phthalic acid 1,2-benzenedicarboxylic acid	benzene-1,3-dicarboxylic acid m-benzenedicarboxylic acid m-dicarboxybenzene m-phthalic acid 1,3-benzenedicarboxylic acid	benzene-1,4-dicarboxylic acid p-benzenedicarboxylic acid p-dicarboxybenzene p-phthalic acid 1,4-benzenedicarboxylic acid
Chemical name (CAS)			
CAS number	88-99-3	121-91-5	100-21-0
Structural formula			
Molecular formula	C ₈ H ₆ O ₄	C ₈ H ₆ O ₄	C ₈ H ₆ O ₄

	phthalic acid	isophthalic acid	terephthalic acid
Volume 25			
Molecular weight	166.13	166.13	166.13
Melting point	230°C, 211°C (SRC 2005; ICSC 2005)	341–348°C (OECD 2002)	207°C (see 1985 documentation, Volume 7, present series)
Boiling point	all isomers decompose at temperatures below the boiling point (see 1985 documentation, Volume 7, present series)		
Vapour pressure	8.5 x 10 ⁻⁷ hPa (25°C; calculated; SRC 2005)	3.5 x 10 ⁻⁸ hPa (25°C; calculated; OECD 2002)	0.01 hPa (20°C; BG Chemie 1990)
log P _{ow} *	0.73 (SRC 2005)	1.66 (SRC 2005)	1.16–2.0 (OECD 2001)
Solubility in water	7010 mg/l (25°C; SRC 2005)	130 mg/l (25°C; SRC 2005)	15 mg/l (20°C; SRC 2005)
pK _a [#] at 25°C	pK _a 1: 2.76 (SRC 2005)	pK _a 1: 3.70 pK _a 2: 4.60 (OECD 2002)	pK _a 1: 3.52 pK _a 2: 4.46 (OECD 2001)

* *n*-octanol/water partition coefficient

dissociation constant

Parts of the MAK documentation for *p*-phthalic acid are based on the 1990 "Toxicological Evaluation" by the BG Chemie.

1 Toxic Effects and Mode of Action

The phthalic acid isomers occur as crystalline, generally white powder. The acute toxicity of the isomers is low.

The isomers are readily absorbed orally (*p*-phthalic acid: about 50%), less readily by inhalation (no other details) and not readily through the skin (*p*-phthalic acid: about 10%). No metabolization has been detected to date. After intravenous injection of [¹⁴C]-*p*-phthalic acid into male F-344 rats, the half-life in the serum was specified to be 1.2 hours and, after oral administration, it was specified to be 2.4 hours.

o-Phthalic acid led to reduced body weight gains in pregnant rats from a dose of 1763 mg/kg body weight and day for a period of 10 days. Other studies on the repeated uptake of *o*-phthalic acid are not available.

No substance-induced findings were observed at concentrations up to 10 mg/m³ after 4-week exposure of rats to *m*-phthalic acid. After 13-week oral administration to rats, an increase in the relative kidney weight from 250 mg/kg body weight and day and the formation of crystals in the urine from 800 mg/kg body weight and day with an increased formation of bladder stones, which might lead to lesions in the bladder, were observed as substance-induced effects.

At 0.5 mg/m³ and more, exposure of rats to *p*-phthalic acid in a 4-week inhalation study led to swelling of lymph nodes and a loss of ciliated cells in the tracheal epithelium exceeding the physiological loss of these cells. In other, incompletely available inhalation studies with exposure duration up to 6 months, no substance-induced findings were observed in the respiratory tract after doses up to 5 mg/m³. After rats ingested *p*-phthalic acid for up to 2 years, mainly the urinary tract, and in some cases also the kidneys, were damaged by crystal and stone formation at doses of 500 mg/kg body weight and day and more. This resulted in tumours in the urinary tract, mainly in the bladder, after prolonged exposure. After exposure to at least 1000 mg *p*-phthalic acid/kg body weight and day, lesions in the bladder occurred particularly in young mice and rats.

No data for irritation are available for *o*-phthalic acid. *m*-Phthalic acid and *p*-phthalic acid produced only slight and reversible irritation to the rabbit eye and skin.

There are no data which suggest that one of the isomers causes sensitization.

The available studies have not shown the isomers to be mutagenic.

In a dominant lethal test, *o*-phthalic acid revealed a reduced number of implantations and sperm anomalies which were induced by cytotoxic effects. There was no evidence of teratogenic effects for any of the three isomers. In studies in which the offspring were also exposed, reduced foetal weights were observed for *o*-phthalic acid and an increased mortality of the offspring for *p*-phthalic acid in a parentally toxic dose range of ≥ 1000 mg/kg body weight and day.

2 Mechanism of Action

Large amounts of phthalic acids taken up orally may lead to high acid concentrations in the urine. As soon as the solubility limit of the phthalic acids in the urine is exceeded, they precipitate in the bladder mainly in the form of calcium terephthalate for example. Calculations have shown that the saturation limit of *p*-phthalic acid in the urine is between 11 and 22 mM in rats and between 8 and 16 mM in humans. This would correspond to an absorption of 2000 mg *p*-phthalic acid/day in humans, assuming a volume of 1.5 l urine excreted/day (Heck and Tyl 1985). It has been assumed that the stones that were formed in animal studies led to lesions via mechanical irritation of the bladder epithelium; depending on the duration of irritation, these may develop into tumours. This assumption is supported by studies in which small inert glass balls were introduced operatively into the urinary bladder of mice or rats, which led to tumours of the bladder wall (Heck and Tyl 1985).

After 14-day administration of 20 mg *p*-phthalic acid/kg body weight and day to Sprague-Dawley rats, the cholesterol and triglyceride levels in the serum of exposed rats were reduced after a single administration of 10 mCi 1,2-³H-cholesterol. The effects of terephthalic acid on *de novo* lipid synthesis showed that the same enzymes were affected in the liver and intestinal mucosa of rats as in *in vitro* cultures of these tissues and in human fibroblasts. The receptor binding to lipoproteins of low density was reduced by *p*-phthalic acid and the degradation of this receptor was increased. *p*-Phthalic acid led to increased receptor binding to lipoproteins of high density and thus to accelerated cholesterol reabsorption from the serum into the liver. Increased excretion of cholesterol and bile acid into the bile was seen in additional studies. The occurrence of elevated serum alkaline phosphatase levels and liver vacuolation in two animals revealed initial changes in the liver (Hall *et al.* 1993).

3 Toxicokinetics and Metabolism

3.1 Absorption, distribution and elimination

After administration of less than 100 mg of one of the isomers to rats, mice, guinea pigs, dogs, cats and humans, the major part of the substance was excreted unchanged mainly in the urine. Major amounts were absorbed only in some cases and the non-absorbed fractions were found in the faeces (BG Chemie 1990).

o-Phthalic acid

After administration of a single intragastric dose of 40 mg/kg body weight or 3.3 mg/kg body weight of radioactively labelled *o*-phthalic acid (no other details) to rats, only 20%–30% was absorbed and excreted unchanged in the urine; the remaining 70%–80%

was found in the faeces (see 1985 documentation “Phthalic acid and its isomers”, Volume 7, present series).

***m*-Phthalic acid**

After 4-week exposure (6 hours/day for 5 days/week) of groups of 10 male and 10 female Sprague-Dawley rats to 1, 5 and 10 mg *m*-phthalic acid/m³ and an observation period of a maximum of 3 weeks, *m*-phthalic acid was detected and quantified by means of HPLC analysis in the serum of the animals exposed (males: 1.44–3.39 µg/ml blood; females: 5.33–9.26 µg/ml blood) throughout the exposure period. One week after the end of exposure, *m*-phthalic acid was no longer detected in the serum of the animals (Amoco Corporation 1988). This study demonstrates that the steady state was reached rapidly and that there was complete elimination within one week.

Groups of 25 young male and 25 female Wistar rats were given a diet containing 0, 0.5%, 1.6% or 5% *m*-phthalic acid for 1 week and then a diet containing 0, 0.5%, 1.6% or 3% *m*-phthalic acid for 12 weeks (corresponding to doses of 0, 250, 800 and 2500 or 1500 µg/kg body weight and day for a rat of 400 g with a feed consumption of 20 g/day). The concentration of *m*-phthalic acid in the blood was determined after 7, 30, 60 and 90 days, was highest in the middle and high dose groups after 7 days (males: 29 and 97.5 µg/ml, respectively; females: 37 and 114 µg/ml, respectively) and then decreased (day 90: males: 17.5 and 26.3 µg/ml, respectively; females: 21.3 and 40.8 µg/ml, respectively). The concentration of *m*-phthalic acid in the urine did not reveal a trend. Since the blood concentration was lower at the end of the study than at the beginning, an adaptive mechanism can be assumed which leads to an accelerated elimination of *m*-phthalic acid (Amoco Chemicals Corporation 1972).

***p*-Phthalic acid**

After oral administration (no other details) of 85 mg [¹⁴C]*p*-phthalic acid/kg body weight to Wistar King A rats, 94% was excreted unchanged in the urine and 3.3% was excreted in the faeces within 48 hours (BG Chemie 1990). In contrast, male rats (no other details) excreted 40% of the radioactivity in the urine and 47% of the radioactivity in the faeces within 48 hours after a single oral administration (no other details) of 40 and 80 mg [¹⁴C]*p*-phthalic acid/animal. After administration of the same doses of *p*-phthalic acid five times within ten days, more than 90% of the radioactivity administered was recovered in the urine and faeces within 48 hours. After intratracheal administration of 5 and 10 mg [¹⁴C]*p*-phthalic acid/animal, less than 1% of the radioactivity was detected in the lungs and the tracheal lymph nodes, and after oral and intratracheal administration, less than 0.1% of the amount administered was recovered in the liver, lungs, heart, kidneys, spleen, adrenals, pancreas, testes, brain and femora (BG Chemie 1990). A plasma clearance of 2.0 ± 0.4 ml/min of [¹⁴C]*p*-phthalic acid was specified for rats, *p*-phthalic acid having been actively excreted via the kidneys and reabsorbed (Heck and Tyl 1985). After intravenous injection of [¹⁴C]*p*-phthalic acid (25 mCi) into male F-344 rats, the half-life in the serum was specified to be 1.2 hours and, after oral administration, it was specified to be 3.4 hours. After intravenous injection, almost 100% was excreted unchanged in the urine within eight hours (OECD 2001).

Ten male Sprague-Dawley rats were exposed to 10 mg *p*-phthalic acid aerosol/m³ on 25 consecutive days and subsequently observed for 28 days to determine the concentration course of *p*-phthalic acid in the blood and urine of the animals. Urine and blood samples were taken on days 1, 5, 10, 15, 18, 22 and 25 during exposure and 7, 14, 21 and 28 days after the end of exposure, and the concentration of *p*-phthalic acid was determined. Urinalysis failed. The quantitative detection limit of *p*-phthalic acid in the blood was 1 µg/ml and was only exceeded on day 15 of chronic exposure (about 1.25 µg/ml). The maximum concentration of *p*-phthalic acid in the blood was 2.7 µg/ml on day 25 of exposure. *p*-Phthalic acid was qualitatively detected for the first time on day 10 (about 0.9 µg/ml) of chronic exposure and up to the last day of the observation period (about 0.5 µg/ml on day 28 after the end of exposure) (Amoco Corporation 1989b).

Groups of 25 young male and female Wistar rats were given a diet containing 0 or 5% *p*-phthalic acid for 1 week and then a diet containing 0 or 3% *p*-phthalic acid for 12 weeks (corresponding to doses of 0 and 2500 or 1500 mg/kg body weight and day for a rat of 400 g with a feed consumption of 20 g/day). The concentration of *p*-phthalic acid in the blood was highest after 7 days (males 75 µg/ml; females 54 µg/ml) and dropped with the duration of exposure (day 90: males 15 µg/ml; females 7 µg/ml), whereas the concentration in the urine increased. This course was continuous in the females, whereas it varied to some extent in the males (Amoco Chemicals Corporation 1972).

After infusion of [¹⁴C]*p*-phthalic acid into the blood vessel leading into the kidneys of hens, a first pass elimination of the unchanged substance was measured in the urine. *p*-Phthalic acid was secreted actively in the primary urine and also reabsorbed actively from it. *p*-Phthalic acid was also actively accumulated in samples from the renal cortex of humans and rats (Tremaine and Quebbemann 1985).

After occlusive dermal application of 80 mg [¹⁴C]*p*-phthalic acid in 0.2 ml aqueous Triton-X solution to the depilated dorsal skin of rats for 24 hours, 5% of the radioactivity was recovered in the urine and faeces and in the lungs, heart, kidneys, spleen, adrenals, pancreas, testes, brain and femora after a single application and 9.4% of the radioactivity after five applications (BG Chemie 1990). When 50 mg [¹⁴C]*p*-phthalic acid was applied into the conjunctival sac of the rabbit eye and rinsed with water after 5 minutes and 24 hours, about 2.5% of the radioactivity was recovered in the above-mentioned organs after a single application and 8.5% after five applications (BG Chemie 1990).

p-Phthalic acid is passed on through the placenta or with breast milk only to a slight extent (Heck and Tyl 1985).

3.2 Metabolism

Phthalic acids are excreted unchanged in the urine and faeces.

o-Phthalic acid

After administration of a single intragastric dose of 40 mg/kg body weight or 3.3 mg/kg body weight of radioactively labelled *o*-phthalic acid to rats, no metabolites were found

(no other details), but 0.15% of the dose administered was exhaled as CO₂ (1985 MAK documentation “Phthalic acid and its isomers”, Volume 7, present series).

There are no data available for *m*-phthalic acid or *p*-phthalic acid.

4 Effects in Humans

There are no data available for the effects of *m*-phthalic acid in humans.

o-Phthalic acid

Among healthy workers exposed to di(2-ethylhexyl)phthalate, the excretion of metabolites with the urine (*o*-phthalic acid: 0.21–0.31 µg/ml; n = 9) was increased as compared with non-exposed workers (*o*-phthalic acid: 0.19 µg/ml; n = 8) (Rettenmeier 1994, 1995). Patients with renal failure are exposed to di(2-ethylhexyl)phthalate during dialysis since it leaches out of the plastic tubes to a slight extent. In the body, di(2-ethylhexyl)phthalate is hydrolyzed mainly to *o*-phthalic acid, which is detected in the serum and dialysate and is excreted unchanged in the urine (Mettang *et al.* 1997, 1999).

p-Phthalic acid

p-Phthalic acid is used as a starting material for the production of polyesters. No damage or toxicity to humans after handling the substance for a prolonged period has been reported (BG Chemie 1990).

Since *p*-phthalic acid is excreted mainly unchanged in the urine and faeces, there may be high concentrations of *p*-phthalic acid in the urine if large amounts are absorbed. As soon as the solubility limit of *p*-phthalic acid in the urine is exceeded, it precipitates preferentially in the bladder mainly in the form of calcium terephthalate. Calculations have shown that the saturation limit of *p*-phthalic acid in the urine is between 8 and 16 mM. According to calculations by the authors, this would correspond to an absorption of 2 g *p*-phthalic acid/day in humans assuming a volume of 1.5 l urine excreted/day (Heck and Tyl 1985).

Local effects on skin and mucous membranes

No signs of erythema or irritation were observed after an oily paste of *p*-phthalic acid (80%) had been applied 10 times to the same skin site of humans. The paste was also tolerated without any signs of erythema or irritation after 24-hour continuous exposure (OECD 2001).

5 Animal Experiments and *in vitro* Studies

5.1 Acute toxicity

5.1.1 Inhalation

There are no data available for *o*-phthalic acid.

m-Phthalic acid

No deaths or treatment-related effects occurred after 4-hour exposure of rats to 11400 mg *m*-phthalic acid/m³ (OECD 2002).

p-Phthalic acid

No rat died after 2-hour exposure of five female and five male Sprague-Dawley rats to 2020 mg *p*-phthalic acid/m³ and a 14-day observation period. The animals had reddened noses and diarrhoea during exposure (Amoco Corporation 1987a).

5.1.2 Ingestion

o-Phthalic acid

The oral LD₅₀ is 7900 mg/kg body weight for rats (Römpf 1999).

m-Phthalic acid

An LD₅₀ in a range of 10400 to 13000 mg/kg body weight was reported in rats (OECD 2002).

p-Phthalic acid

The data for the LD₅₀ are between > 1900 mg/kg body weight and 18800 mg/kg body weight in rats (OECD 2001). In mice the LD₅₀ is > 5000 mg/kg body weight, in female Swiss mice the LD₅₀ is 1470 mg/kg body weight (BG Chemie 1990).

5.1.3 Dermal absorption

There are no data available for *o*-phthalic acid.

***m*-Phthalic acid**

None of four rabbits died after application of *m*-phthalic acid doses of 23000 mg/kg body weight or up to the end of the observation period after 14 days (OECD 2002).

***p*-Phthalic acid**

No lethal effect occurred after occlusive application of 500 mg *p*-phthalic acid/animal to the clipped dorsal skin of 3 male and 3 female albino New Zealand rabbits for 4 hours (Amoco Corporation 1990b).

A *p*-phthalic acid dose of 2000 mg/kg body weight was applied to the clipped dorsal skin of five male and five female albino New Zealand rabbits and remained in occlusive contact for 24 hours. Afterwards the substance was removed and the animals were observed for 14 days. No animal died (Amoco Corporation 1990c).

5.1.4 Other routes of administration

There are no data available for other routes of administration of *o*-phthalic acid.

***m*-Phthalic acid**

The LD₅₀ after intraperitoneal administration was 13000 mg/kg body weight in rats (OECD 2002).

***p*-Phthalic acid**

The LD₅₀ after intraperitoneal injection was 1210 mg/kg body weight in female rats and 2250 mg/kg body weight in male rats. An LD₅₀ between 880 and 1900 mg/kg body weight was found in mice after intraperitoneal administration (BG Chemie 1990).

The intravenous injection of *p*-phthalic acid resulted in an LD₅₀ of 770 mg/kg body weight for female Swiss mice and of 767 mg/kg body weight for mongrel dogs (BG Chemie 1990).

5.2 Subacute, subchronic and chronic toxicity

5.2.1 Inhalation

There are no data available for *o*-phthalic acid.

***m*-Phthalic acid**

After 4-week exposure (6 hours/day for 5 days/week) of groups of ten male and ten female Sprague-Dawley rats to *m*-phthalic acid concentrations of 0, 1, 5 and 10 mg/m³ carried out according to OECD Test Guideline 412, slight redness around the eyes and

nose was observed in some animals. No treatment-related effects were seen in body weight gain, organ weights, haematology or clinico-chemical parameters. No effects, not even in the nose or trachea, were observed in the histopathological examination. Additional animals were observed for a maximum of 3 weeks; *m*-phthalic acid was no longer detected in the serum one week after the end of the study (Amoco Corporation 1988). The no observed adverse effect concentration (NOAEC) was therefore 10 mg/m³.

***p*-Phthalic acid**

The phospholipid level of the surfactant was determined in the bronchioalveolar lavage fluid after exposure of Sprague-Dawley rats to a medium *p*-phthalic acid concentration of 8.9, 274.5 and 618.1 mg/m³. There was a statistically significant lowering of phosphatidylcholine, phosphatidylglycerol and phosphatidylinositol in the middle and high dose groups. It was assumed that the type II cells of the pulmonary epithelium producing the surfactant were damaged by *p*-phthalic acid (no other details in the abstract; publication in Chinese; Shi *et al.* 2000).

After exposure of five male and five female Sprague-Dawley rats to *p*-phthalic acid concentrations of 2020 mg/m³ (aerosol particles of unknown size) for a period of 2 hours per day and 5 days per week for two weeks, diarrhoea, redness around the nose and wet or discoloured fur of the abdominal and inguinal regions were observed. At necropsy, one male and one female rat revealed enlarged lymph nodes in the lower jaw and one male rat had dark areas in the lungs. No other changes were reported (Amoco Corporation 1987a). A NOAEC was not obtained. The nose and trachea were presumably examined gross-pathologically, but there is no list of which organs were examined.

Ten animals were exposed to *p*-phthalic acid aerosol containing 10 mg/m³ on 25 consecutive days and subsequently observed for 28 days to determine the course of the change in concentration of *p*-phthalic acid in the blood and urine of male Sprague-Dawley rats (see Section 3.1). Blood analyses and urinalyses were carried out before the beginning of exposure and on exposure days 1, 5, 10, 15, 22 and 25 as well as on days 7, 14, 21 and 28 after the end of exposure. No adverse effects were observed in the animals during or after the end of exposure or at necropsy carried out at the end of the observation period (Amoco Corporation 1989b). This study yielded a NOAEC of 10 mg/m³, but no histopathological examination was reported.

Body weight gain was reduced after 4-week whole-body exposure of ten male Wistar rats to *p*-phthalic acid concentrations of 25 mg/m³ (aerosol particles with a mean diameter of 2.3 µm; 6 hours per day for 5 days a week): The body weight of five animals was hardly changed during the exposure period, and the remaining animals gained up to 28 g. The *p*-phthalic acid concentration in the blood and urine was higher than calculated on the basis of the inhalation. It is therefore assumed that the substance was also ingested orally by the animals licking their fur. The pathological examination of the animals exposed revealed no changes. There are however no data of whether the trachea was also examined (Standard Oil Company 1973). No concurrent control group was included, nor was a NOAEC obtained.

No toxicologically relevant findings (no other details) were obtained from a 4-week inhalation study in rats which had been exposed to *p*-phthalic acid concentrations of 225 mg/m³ 6 hours per day on 5 days per week (BG Chemie 1990).

Male and female Sprague-Dawley rats were exposed to *p*-phthalic acid doses of 0, 0.52, 1.19 and 3.31 mg/m³ for 6 hours/day 5 days/week (whole body) for 4 weeks; 98.7% of the particles were ≤ 10 μ m and could thus be inhaled. 16 animals/sex were used in the highest dose and control groups, and 10 animals/sex were used in each of the two other dose groups. No specific symptoms were observed in the animals exposed. Non-specific observations included salivation in three animals, one of them from the control group, redness around the eyes in one or two animals per group and redness of the nose in 5 to 14 animals per group (not dose-related; controls: 9/32). Body weights, body weight gains and organ weights did not differ significantly from those of the control group. Haematological and clinico-chemical examinations revealed no significant differences between exposed animals and control animals. The lung function parameters of the animals exposed were the same as those of the controls at rest and with physical exercise. The histopathological examination yielded degeneration of the tracheal epithelium in 19 of 20 animals of the highest exposure group, in 13 of 20 of the middle group, in 6 of 20 of the lowest group and in 1 of 20 animals of the control group. The number of sites of degeneration increased with the dose, but the severity did not change (always severity 1 to 4). No effects were observed in the nose. The female rats of all dose groups revealed an increase in haemorrhages in the lymph nodes of the respiratory tract (controls: 3/10; animals exposed: 6/10), and in male rats there was an increase in hyperplasia of the plasma cells in the lymph nodes of the lower jaw in all dose groups (controls: 2/10; animals exposed: 5/10; Amoco Corporation 1987b). The overall result of the histopathological examinations provided no evidence of systemic toxicity. Haematology, clinical chemistry and respiratory physiology were not affected. Histopathologically, minimal degenerative changes, the incidence of which increased with an increasing concentration, were found locally in the tracheae of both sexes. The alterations in the respiratory epithelium of the trachea were specified in more detail as a reduction of ciliated cells, a certain randomness of the cells in the epithelium and occasionally slight hyperplasia of the epithelium. The severity of these alterations did not increase although the incidence was higher. The degree "minimal" means that there was a very slight deviation from normal, which is only detected by pathologists who are experienced in the area of the respiratory tract. Nevertheless, there was a substance-induced change which showed a dose-response-specific progression. On the basis of the unchanged systemic parameters (especially haematology and respiratory physiology), the changes observed at the two lower dose levels can be regarded as slight.

Male Sprague-Dawley rats and male Hartley guinea pigs were exposed to *p*-phthalic acid dust at a concentration of 10 mg/m³ for 6 hours/day 5 days/week for 6 months. The inhalable dust concentration was 5 mg/m³. At examinations after 30, 60 and 140 exposures, body weight gains and organ weights were the same in exposed and non-exposed animals. Clinico-chemical and urine parameters and gross-pathological and histopathological examinations revealed no changes compared with the control animals (Lewis *et al.* 1982). A NOAEC of 5 mg/m³ was obtained in this study. The individual

data were however not listed in the abstract. No other publications by these authors on this subject were found.

5.2.2 Ingestion

o-Phthalic acid

In a prenatal developmental toxicity study (see Section 5.5.2), pregnant Wistar rats were given 0, 1.25%, 2.5% and 5% *o*-phthalic acid with the diet on days 7 through 16 of pregnancy. The average daily ingestion of *o*-phthalic acid was 1021, 1763 and 2981 mg/kg body weight and day. The dams showed significantly reduced body weight gains and significantly reduced feed consumption in the middle and high dose groups. No observations of this kind were made in the low dose group. No lethal effects or additional clinical findings were observed (Ema *et al.* 1997).

m-Phthalic acid

Young Wistar rats were given a diet containing 0, 0.5%, 1.6% and 5% *m*-phthalic acid for a period of one week and then a diet containing 0, 0.5%, 1.6% and 3% *m*-phthalic acid for 12 weeks (about 250, 800 and 2500 or 1500 mg *m*-phthalic acid/kg body weight and day). All animals survived. The findings are listed in Table 1. At 800 mg/kg body weight and above, the urinalysis carried out on exposed animals on days 30, 60 and 90 revealed an elevated concentration of red blood cells in the urine in increasingly more animals with increasing exposure duration and small crystals of the test substance in all animals exposed from day 60 of the study. On day 90 of the study, the incidence of crystals in the urine was lower than on day 60 of the study. The haematological and clinico-chemical parameters revealed no substance-induced findings, and the ratio of organ to body weights or organ to brain weights was changed only in the females of the highest dose group with regard to the kidneys. The histopathological examination revealed slight hydronephrosis at 800 mg/kg body weight and more; no other findings were observed (Amoco Chemicals Corporation 1972). The no observed adverse effect level (NOAEL) related to kidney changes (the most sensitive parameter) was 0.5% *m*-phthalic acid (250 mg/kg body weight and day) in this study.

p-Phthalic acid

The individual findings of the studies reviewed below are listed in Table 1.

After 14-day administration of 0 or 20 mg *p*-phthalic acid/kg body weight and day to male Sprague-Dawley rats, the cholesterol and triglyceride levels in the serum of exposed rats were reduced after a single administration of 10 mCi 1,2-³H-cholesterol. Only parameters of the lipid metabolism were examined (see Section 2; Hall *et al.* 1993).

Table 1. Effect of individual phthalic acid isomers after repeated oral administration

Species, strain, number of animals, sex/group	Exposure	Findings	References
<i>m</i>-phthalic acid			
Wistar rats, groups of 25 ♂, 25 ♀	13 weeks, 0, 0.5%, 1.6%, 5% in the diet for 1 week, then 0, 0.5%, 1.6%, 3% in the diet for 12 weeks (about 0, 250, 800, 2500 or 1500 mg/kg body weight and day)	from day 30 of study onwards: increased amount of blood cells in the urine ≥ 800 mg/kg body weight and day: day 60 of study: crystals in the urine increased; hydronephrosis; ♂: 1 animal with bladder stone per dose group 1500 mg/kg body weight and day: urine more acidic than that of control animals ♂: feed consumption reduced; body weight gains reduced ♀: relative kidney weights increased; 1 animal with a kidney stone NOAEL: 250 mg/kg body weight and day LOAEL: 800 mg/kg body weight and day	Amoco Chemicals Corporation 1972
<i>p</i>-phthalic acid			
Fischer 344 rats, groups of 10 weanling ♂, 10 weanling ♀	2 weeks, 0, 0.5%, 1.5%, 3%, 4%, 5% in the diet (about 0, 1250, 3750, 7500, 10000, 12500 mg/kg body weight and day)	pH of urine 5.7 (control 6.3); Ca ²⁺ and PO ₄ ³⁻ in the urine increased ≥ 7500 mg/kg body weight and day: dose-dependent formation of bladder stones; animals with bladder stones: hyperplasias of bladder wall epithelium and haematuria ≥ 10000 mg/kg body weight and day: body weight gains reduced; drinking water consumption increased NOAEL: 1250 mg/kg body weight and day	Chin <i>et al.</i> 1981
Fischer 344 rats, groups of 10 ♂	2 weeks, 0, 4% in the diet (about 0, 10000 mg/kg body weight and day)	body weights reduced by 20% 5/10 bladder stones; urine: hyperacidic; Ca ²⁺ and Mg ²⁺ levels increased	Wolkowski-Tyl and Chin 1983
Wistar rats, groups of 25 ♂, 25 ♀	1 week, 0, 5% in the diet, then 12 weeks, 0, 3% in the diet (about 0, 2500 or 1500 mg/kg body weight and day)	feed consumption reduced; body weight gains reduced; urine: from day 30: blood, red blood cells increased; from day 60: crystals ♀: 3/19 bladder stones; 1/19 kidney stone; 4/19 bladder epithelium hyperplasias ♂: 11/18 bladder stones; 13/18 bladder epithelium hyperplasias	Amoco Chemicals Corporation 1972

Table 1. continued

Species, strain, number of animals, sex/group	Exposure	Findings	References
Sprague-Dawley and Wistar rats, groups of 20 ♂, 20 ♀	90 days, 0, 0.03%, 0.125%, 0.5%, 2%, 5% in the diet (about 0, 15, 63, 250, 1000 and 2500 mg/kg body weight and day)	bladder stones after 90 days: Wistar ♂: 15 mg/kg body weight and day: 1/10 2500 mg/kg body weight and day: 4/10 ♀: 2500 mg/kg body weight and day: 1/10 Sprague-Dawley: ♂: no bladder stones ♀: 2500 mg/kg body weight and day: 1/10 hyperplasias of bladder transitional cells: 2500 mg/kg body weight and day: Wistar ♂: 3/9 ♀: 5/10 Sprague-Dawley ♂: 1/10 ♀: 4/10	CIIT 1982
Sprague-Dawley rats, 17 or 18 ♂/♀	90 days, 0, 50, 500, 5000 mg/kg body weight and day	0 mg/kg body weight and day: single hyperplasia 1/18 50 mg/kg body weight and day: single hyperplasia 10/17 500 mg/kg body weight and day: 2/18 bladder stones; 10/17 atypical hyperplasia; 5/18 single hyperplasia 5000 mg/kg body weight and day: 10/17 bladder stones; 4/17 tumours of bladder transitional cells; 5/17 atypical hyperplasia; 7/17 single hyperplasia	Qi <i>et al.</i> 2002
albino rats, groups of 30 ♂, 30 ♀	15 weeks, 2×0, 0.05%, 0.16%, 0.5%, 1.6%, 5% in the diet (♀ about 0, 46, 146, 460 or 4600 mg/kg body weight and day; ♂ about 0, 38, 122, 380 or 3800 mg/kg body weight and day)	at 5%: body weight gains reduced with comparable feed consumption; haematuria ♂: lesions of the bladder epithelium; bladder stones: 3/3 after 30 days, 2/3 after 60 days, 2/3 after 90 days and 9/17 after 105 days p-phthalic acid in the blood (detection limit 5 µg/ml): determinable in the three highest dose groups after 4 weeks, at the end only in highest dose group in ♂ and in two highest in ♀ p-phthalic acid in the urine (detection limit 10 µg/ml): ♂: 38 mg/kg body weight and day: 40 µg/ml 3800 mg/kg body weight and day: 3780 µg/ml ♀: 146 mg/kg body weight and day: 40 µg/ml 4600 mg/kg body weight and day: 7020 µg/ml NOAEL: ♂ about 1220 mg/kg body weight and day ♀ about 1456 mg/kg body weight and day	Amoco Chemicals Corporation 1970

Table 1. continued

Species, strain, number of animals, sex/group	Exposure	Findings	References
Wistar rats, groups of 50 ♂, 50 ♀	2 years, 0, 1%, 2%, 5% in the diet (0, 20, 142, 1000 mg/kg body weight and day)	0 mg/kg body weight and day: ♀: neoplasms in the urogenital tract 20 mg/kg body weight and day: absolute kidney weights reduced; ♂: 1/43 bladder and ureter neoplasms ♀: absolute liver weights decreased; 1/48 bladder stones; neoplasms in the urogenital tract 142 mg/kg body weight and day: absolute liver weights decreased; ♂: body weight gains reduced; 1/48 bladder and ureter neoplasms ♀: absolute heart weights decreased; 2/47 bladder and ureter neoplasms 1000 mg/kg body weight and day: body weight gains reduced; mortality increased from the 2nd month (stone formation → nephrohydrosis → urinary tract infection); adrenal weights increased; epithelial changes in the urinary tract: hyperplasias; papillomas; scaly metaplasias; squamous metaplasias and carcinomas; tumours of the transitional cells ♂: absolute kidney weights increased; 42/47 bladder stones; 21/37 bladder and ureter neoplasms ♀: 39/42 bladder stones; 21/34 bladder and ureter neoplasms	BG Chemie 1990; OECD 2001
Fischer 344 rats, groups of 26 ♂, 26 ♀	2 years, 0, 20, 142, 1000 mg/kg body weight and day	1000 mg/kg body weight and day: urinary pH decreased; absolute kidney weights decreased; 19/118 bladder tumours (assessed mainly as hyperplasias by a 2nd laboratory) ♀: 12/86 bladder stones NOAEL: 142 mg/kg body weight and day	CIIT 1983a, 1983b

Fischer 344 weanling rats (55–110 g body weight) received diets containing 0, 0.5%, 1.5%, 3%, 4% and 5% *p*-phthalic acid (corresponding to about 0, 1250, 3750, 7500, 10000 and 12500 mg/kg body weight and day for a rat of 80 g with a feed consumption of 20 g/day) for a period of two weeks to investigate the formation of bladder stones. At *p*-phthalic acid doses of 3750 mg/kg body weight and day, hyperacidic urine, increased calcium excretion in the urine and bladder stone formation were observed, males being affected more than females. It is assumed that the increasing acidity of the urine led to reduced absorption of calcium in the renal tubules. Histopathological changes in the

bladder were observed only in animals with bladder stones (Chin *et al.* 1981). The NOAEL obtained in this study was 0.5% *p*-phthalic acid in the diet (about 1250 mg/kg body weight and day).

When weanling male Fischer 344 rats were given 0 and 4% *p*-phthalic acid in the diet for two weeks (about 10000 mg/kg body weight and day), there was a weight reduction of 20%. 50% of the animals had bladder stones mainly in the lumen of the urinary bladder. The urine was hyperacidic and the calcium and magnesium levels in the urine were increased (Wolkowski-Tyl and Chin 1983).

Young Wistar rats were given diets containing 0 and 5% *p*-phthalic acid for a period of one week and then diets containing 0 and 3% *p*-phthalic acid for 12 weeks (corresponding to doses of 0 and 2500 or 1500 mg/kg body weight and day for a rat of 400 g with a feed consumption of 20 g/day). One treated animal died from a respiratory tract infection; no other deaths occurred. Primarily bladder stones and hyperplasias of the bladder epithelium, which showed no signs of neoplastic changes, were observed. There was a close correlation between the incidences of hyperplasia and bladder stones (Table 1). The parameters for relative organ weight and organ/brain weight and the haematological and clinico-chemical blood parameters were normal; nor were any other findings observed in the histopathological examination (Amoco Chemicals Corporation 1972). No NOAEL was obtained from this study.

In a comparative 90-day feeding study, male and female Sprague-Dawley (mean body weight of males 420 g and of females 305 g) and Wistar rats (mean body weight of males 400 g and of females 620 g) were given 0, 0.03%, 0.125%, 0.5%, 2% and 5% *p*-phthalic acid in the diet (corresponding to doses of 0, 15, 63, 250, 1000 and 2500 mg/kg body weight and day for a rat of 400 g with a feed consumption of 20 g/day). The results showed that male Wistar rats were more susceptible to the development of bladder stones (Table 1) (CIIT 1982). No NOAEL was obtained from this study.

Sprague-Dawley rats were given *p*-phthalic acid doses of 0, 50, 500 and 5000 mg/kg body weight and day for 90 days. Bladder stones and lesions in the bladder epithelium including tumours were observed as main effects (Table 1). The authors summarized that, in this study, there was a positive correlation between pathological changes and the dose, but no correlation between bladder stone incidences and pathological changes in the bladder (no other details in the abstract; publication in Chinese; Qi *et al.* 2002). This study yields no NOAEL.

Albino rats were exposed to 0, 0.05%, 0.16%, 0.5%, 1.6% and 5% *p*-phthalic acid in the diet (60 animals per dose group; 2 control groups; ♀: about 0, 46, 146, 460 and 4600 mg/kg body weight and day; ♂: about 0, 38, 122, 380 and 3800 mg/kg body weight and day) for 15 weeks. The concentrations of *p*-phthalic acid were determined in the blood and urine (Table 1). Slightly reduced body weight gains (with feed consumption being comparable with that of the control animals) and, mainly in the males, haematuria, bladder stones and lesions of the bladder epithelium were observed as substance-induced effects only in the highest dose group (Amoco Chemicals Corporation 1970). The NOAEL was thus 1.6% *p*-phthalic acid in the diet (about 1220 mg/kg body weight and day for males and 1456 mg/kg body weight and day for females).

In a two-year study with male and female Wistar rats, 0, 1%, 2% or 5% *p*-phthalic acid was administered in the diet (0, 20, 142 and 1000 mg/kg body weight and day). The findings, mainly formation of urinary calculi and resulting lesions of the urinary tract epithelium, are listed in Table 1. Neoplasms in the urogenital tract were detected in the females of the low dose group and of the control group. Exposure to *p*-phthalic acid reduced the rate of mammary tumours in the females and the rate of carcinomas of the thyroid medulla in the males (BG Chemie 1990; OECD 2001). No NOAEL was obtained in this study.

p-Phthalic acid doses of 0, 20, 142 and 1000 mg/kg body weight and day were administered to male and female F-344 rats in the diet for a period of two years. Body weight gains, feed consumption, clinico-chemical parameters, haematology, urinalyses, ophthalmological and neurological measurements, pathology after 6, 12, 18 and 24 months, organ weights and histopathology were normal. There were only slight substance-induced effects in the highest dose group (Table 1 and Section 5.7). Cataracts and retinal lesions and, in the females, adenomas or adenocarcinomas of the uterus in exposed and non-exposed animals were observed as effects not induced by the substance. The histopathological examinations were carried out by two different institutes, which arrived at different assessments: The lesions of the bladder classified as “adenomas of the transitional cells” by the pathologists of the institute carrying out the experiment were assessed mainly as “hyperplasias of the epithelium” by another institute. The unusually high incidence of eye lesions and adenomas of the uterus observed in the animals in these studies was explained by the authors by the fact that a problem with the illumination of the animal rooms was detected 18 months after the beginning of the study. It is not known how long the animals were possibly exposed to a more than 12-hour light phase. The authors pointed out that retinal lesions occur in rats as early as after 10-day constant illumination. Synchronization of the female cycle of rats is also regulated by light. If there is continuous illumination, rats remain in the oestrus phase with increased oestrogen levels. It has been demonstrated that oestrogen levels increased for a prolonged period lead to hyperplasias and sometimes also to tumours in the uterus (CIIT 1983a, 1983b). If the explanations of the authors are followed, a substance-induced NOAEL of 142 mg/kg body weight and day is obtained.

5.2.3 Other routes of absorption

***o*-Phthalic acid**

The stimulating or inhibitory effect of *o*-phthalic acid on the immune system of mice after subcutaneous injection was investigated in a murine injection model. For this purpose, ovalbumin was injected alone (control) or together with *o*-phthalic acid (test substance), benzyl alcohol (test substance) or aluminium hydroxide (positive control). After the reaction had been intensified by one or two injections of ovalbumin, blood was removed from the animals and investigated for the ovalbumin-specific antibodies IgE, IgG1 or IgG2a by enzyme-linked immunosorbent assay (ELISA) methods. Immuno-

suppression was seen with benzyl alcohol, whereas *o*-phthalic acid had no effect (Larsen *et al.* 2003).

There are no data available for other routes of absorption of ***m*-phthalic acid**.

***p*-Phthalic acid**

Ten female rats were injected intraperitoneally with a dose of 1.1 g *p*-phthalic acid per animal (15% *p*-phthalic acid in olive oil) on every 7th day over a period of 102 days. The animals behaved normally; body weight gains were reduced compared with the control group from the 6th week. No pathological findings were obtained at the end of the study (BG Chemie 1990).

No data are available for subacute, subchronic or chronic toxicity via dermal absorption of any of the isomers.

5.3 Local effects on skin and mucous membranes

5.3.1 Skin

There are no data available for ***o*-phthalic acid**.

***m*-Phthalic acid**

In a study to determine the dermal LD₅₀, 2000 mg/kg body weight was applied occlusively to the shaved dorsal skin of 5 male and 5 female rabbits. Slight erythema was observed on 4 animals immediately after removal of the coverings. Necropsy revealed no treatment-related changes (OECD 2002).

***p*-Phthalic acid**

No irritation was induced by *p*-phthalic acid after 48-hour semioclusive contact of an aqueous suspension of 80 mg *p*-phthalic acid in 0.2 ml water to the skin of rats (applied 5 times in 10 days) (BG Chemie 1990).

After occlusive application of 500 mg *p*-phthalic acid/animal to the shaved dorsal skin of 3 male and 3 female New Zealand albino rabbits for 4 hours, the skin was slightly reddened immediately after removal of the substance (score 0.2/8.0). Erythema had disappeared by the end of the observation period after 72 hours (Amoco Corporation 1990b).

p-Phthalic acid at a dose of 2000 mg/kg body weight was applied to the shaved dorsal skin of 5 male and 5 female New Zealand albino rabbits and remained in occlusive contact for a period of 24 hours. Afterwards the substance was removed and the animals were observed for 14 days. Slight erythema was observed on 6 rabbits immediately after removal of the substance. At the end of the observation period, the backs of the rabbits were normal and covered with hair again (Amoco Corporation 1990c).

5.3.2 Eyes

There are no data available for ***o*-phthalic acid**.

***m*-Phthalic acid**

Three different studies revealed no irritation to the eyes. 24 hours after application of 100 mg *m*-phthalic acid to one eye, there was slight redness (maximum score from three studies 25.6 of 110), which disappeared after 4 days at the latest (OECD 2002).

***p*-Phthalic acid**

The application of 100 mg undiluted *p*-phthalic acid to one eye of each of six albino rabbits led to slight irritation of the iris and conjunctiva, which was 9.0 of a total score of 110 after one hour and 4.5 after 24 hours. All symptoms had disappeared 48 hours after application (Standard Oil Company 1975). This result was confirmed in another study with three rabbits in which the maximum score was 10 of 110 (Amoco Corporation 1990a).

5.4 Allergenic effects

There are no data available for ***o*-phthalic acid**.

***m*-Phthalic acid**

m-Phthalic acid was negative in a sensitization test (modified Bühler test) (OECD 2002).

***p*-Phthalic acid**

According to a screening study, *p*-phthalic acid is not sensitizing to humans (no other details) (BG Chemie 1990). Nor was *p*-phthalic acid sensitizing in a test for sensitization in guinea pigs (OECD 2001).

5.5 Reproductive toxicity

5.5.1 Fertility

There are no data available for the effects of ***o*-phthalic acid** or ***m*-phthalic acid**.

***p*-Phthalic acid**

Groups of 10 male Sprague-Dawley rats were given 0, 0.2%, 1% and 5% *p*-phthalic acid in the diet (about 100, 500 and 2500 mg/kg body weight and day), and the functions of the testes were examined after 90-day treatment. The treated animals did not reveal loss of body weight or reduced testis weight. Lesions in spermatogonia and Sertoli cells and a significant reduction of sperm production, testicular sperm head counts and in the activity of sorbitol dehydrogenase were observed in the highest dose group. The motility of spermatozoa was significantly reduced in relation to the dose in all treated groups. The serum testosterone concentrations were not affected in the animals exposed (Cui *et al.* 2004).

In a one-generation study, 0, 0.03%, 0.125%, 0.5%, 2% or 5% *p*-phthalic acid were administered in the diet to Wistar and CD rats of both sexes 90 days before mating, during mating and to females up to the end of the lactation phase (male CD rats: 0, 14, 59, 240, 930 and 2499 mg/kg body weight and day; female CD rats: 0, 17, 67, 282, 1107 and 2783 mg/kg body weight and day; male Wistar rats: 0, 14, 61, 249, 960 and 2480 mg/kg body weight and day; female Wistar rats: 0, 19, 78, 307, 1219 and 3018 mg/kg body weight and day). Ten male and ten female animals were mated per dose group. Reduced feed consumption was observed in the female parental CD rats in the two highest dose groups and in the parental Wistar rats in the highest dose group. After 13 weeks, the body weights of the parental animals were statistically significantly reduced at 5% *p*-phthalic acid in the diet in Wistar rats and even from 2% in the diet in CD rats. Reduced body weight was also seen in male CD rats after administration of 0.03% *p*-phthalic acid in the diet. Three CD rats (one male of the 2% and one male and one female of the 5% dose group) and four female Wistar rats (two of the 5% and two of the 0.03% dose group) of the parental animals died. Further observations or findings in the parental animals were not reported in the available publication. There were no effects of *p*-phthalic acid on the end points of fertility index, sex ratio or litter size, but the pup mortality was clearly increased in the animals exposed: 16 young Wistar rats (1 of the 0.03%, 2 of the 0.125%, 1 of the 0.5% and 12 of the 2% dose group) and 23 young CD rats (1 of the 0.05%, 7 of the 2% and 15 of the 5% dose group) died on the day of birth. No pup of the control group died. The survival rate of the pups was reduced in the two highest dose groups on day 21. Some litters died from maternally toxic effects since the dams did not allow their pups to nurse or did not care for the litters. The pups that died in this way had no milk in their stomachs at necropsy. The dams affected were exposed to doses of *p*-phthalic acid known to cause reduced feed consumption, diarrhoea and gastric trichobezoars (hair balls in the gastrointestinal tract) and to induce the formation of renal and bladder stones. The body weights of the pups of the highest dose group were significantly lower than those of the control animals on day 1 (Wistar rats only) and on day 21 (both strains). Half of the pups were examined after 21 days, renal and bladder stones being noted in all animals of the highest dose group. The remaining pups were examined on day 51. After weaning, these animals ingested the same diet as the parental animals for 30 days and were therefore exposed to higher doses than the parental animals in relation to body weight. 18 Wistar and 16 CD pups died between days 21 and 51. Renal and bladder stones were detected in the pups of the highest dose group. At the

necropsy of the pups on day 51, enlarged caecum, enlarged or distended urethra, enlarged kidneys and thickening of the bladder wall were noted in the animals treated with more than 0.5% *p*-phthalic acid. There were no differences in sensitivity to *p*-phthalic acid between the rat strains. The NOAEL for parental animals and their offspring was 0.5% *p*-phthalic acid in the diet (240–307 mg/kg body weight and day) (CIIT 1982; BG Chemie 1990; OECD 2001).

Female CF1 mice were intraperitoneally injected with *p*-phthalic acid doses of 0, 20, 50 and 100 mg/kg body weight and day for six weeks. During the last three weeks, the animals were mated with non-exposed males, one male remaining with two females for one week in each case. The substance had no effect on pregnancy, the number of litters or birth weight. The number of live pups was slightly reduced at 50 mg/kg body weight and day after three weeks, but the weights of the pups were in the normal range (Hall *et al.* 1993).

5.5.2 Developmental toxicity

o-Phthalic acid

In a prenatal developmental toxicity study, pregnant Wistar rats were given 0, 1.25%, 2.5% or 5% *o*-phthalic acid with the diet on gestation days 7 through 16. The average daily ingestion of *o*-phthalic acid was 1021, 1763 and 2981 mg/kg body weight and day in the three dose groups. Maternal toxicity was observed in the middle and high dose groups as shown by significantly reduced body weight gains and significantly reduced feed consumption in the dams during exposure. No observations of this kind were made in the low dose group. No lethal effects or clinical findings were observed in the dams. No significant changes were detected in the incidences of postimplantation loss or sex ratio of live foetuses. The weight of the male foetuses was significantly reduced in the highest dose group and ossification of the caudal vertebrae was retarded. The morphological examination of the foetuses revealed no evidence of teratogenic effects (Ema *et al.* 1997).

m-Phthalic acid

In a prenatal developmental toxicity study, groups of 16 to 18 pregnant Sprague-Dawley rats were exposed to *m*-phthalic acid aerosol concentrations of 0, 0.98, 4.23 or 9.07 mg/m³ on gestation days 6 through 15 for 6 hours per day 7 days per week. No animal died. No statistically significant differences were noted between control and exposed animals in body weight gain, uterus or litter weight, clinical examinations, the number of live foetuses or the incidence of malformations (OECD 2002). The concentrations used were so low that neither maternal nor developmental toxicity was observed.

p-Phthalic acid

In a segment II study, groups of 22 to 25 pregnant Sprague-Dawley rats were exposed to *p*-phthalic acid concentrations of 0, 0.9, 4.73 or 10.4 mg/m³ for 10 days on gestation

days 6 through 15. There were no deaths or any abnormal clinical signs in the animals exposed. No statistically significant differences between exposed and non-exposed animals were noted in the body weight gains of the dams, the uterus or litter weights or the survival of the offspring. The examinations of the foetuses for externally evident changes and organ changes revealed no significant differences between exposed and non-exposed animals for malformations or anomalies. A slight increase in the number of foetuses with rib anomalies in the middle dose group was not assessed by the authors as a substance-induced effect since the effect was not dose-related and the specific values were within the range of the laboratory's historical controls. Therefore, the concentrations of *p*-phthalic acid used in this inhalation study revealed neither maternal nor developmental toxicity. The NOAEL was 10 mg/m³ (Amoco Corporation 1989a).

In a study on the fertility of Sprague-Dawley and CD rats (see Section 5.5.1), the pups which received more than 0.5% *p*-phthalic acid (240–307 mg/kg body weight and day) revealed enlarged caeca, distended urethras, enlarged kidneys and a thickened bladder wall. The NOAEL for both rat strains was 0.5% *p*-phthalic acid in the diet (240–307 mg/kg body weight and day) (BG Chemie 1990; OECD 2001).

5.6 Genotoxicity

The available studies have not shown the isomers to be genotoxic.

5.6.1 *In vitro*

There are no data available for *o*-phthalic acid.

m-Phthalic acid

Various studies with *Salmonella typhimurium* strains in the presence and absence of a metabolic activation system from rat livers showed that *m*-phthalic acid was mainly negative in concentrations up to and including 1000 µg/plate. Precipitation of the test substance was reported in concentrations ≥ 5000 µg/plate. Nevertheless, concentrations up to 10000 µg/plate, which led to increased mutation rates in some cases, were tested by two of three working groups. TA98, TA100, TA1535, TA1537 and TA1538 were the *S. typhimurium* strains used by all working groups. The working group which tested concentrations up to 5000 µg/plate observed no increased mutation frequencies (OECD 2002).

The positive results are not used for assessment since it is assumed that *m*-phthalic acid precipitated at these concentrations and the effect cannot be attributed to *m*-phthalic acid that had dissolved.

m-Phthalic acid did not lead to an increase of chromosome aberrations in tests with CHO cells (a cell line from Chinese hamster ovary) in the presence or absence of a metabolic activation system even at concentrations of 5000 µg/l. Hypoxanthine guanine phosphoribosyl transferase (HPRT) gene mutation tests with CHO cells and

concentrations up to 3000 µg/l were also negative. Nor was *m*-phthalic acid mutagenic in the gene mutation test with mouse lymphoma cells in concentrations up to 950 µg/l (OECD 2002).

***p*-Phthalic acid**

No mutagenic effect was found in various studies with *Salmonella typhimurium* TA97, TA98, TA100, TA102, TA1535, TA1537 and TA1538 in the presence or absence of a metabolic activation system up to concentrations of 3 µmol/plate or 10 mg/plate. Since precipitation was observed in some studies at 10 mg/plate, no higher doses were tested (OECD 2001).

In tests with *Salmonella typhimurium*, *p*-phthalic acid was not positive at any of the concentrations used of 0, 0.5, 5, 50 or 500 µg/ml in the unscheduled DNA synthesis (UDS) test with primary rat hepatocytes or in the test for micronuclei in human lymphocytes (Lerda 1996). No cytotoxic effects were observed in any of the studies.

5.6.2 *In vivo*

***o*-Phthalic acid**

A test for dominant lethal mutations was carried out with 20 male Swiss albino mice per dose group. The animals received a single intraperitoneal injection of either 0, 40 or 80 mg *o*-phthalic acid/kg body weight in 10% DMSO on five consecutive days and were mated with untreated females for four weeks. The females remained with the males for one week so that offspring were produced 1–7 days, 8–14 days, 15–21 days or 22–28 days after treatment with *o*-phthalic acid. The number of implantations was significantly reduced in the third and also in the fourth week after treatment and the incidence of dominant lethal mutations was increased (Jha *et al.* 1998). This positive dominant lethal test is not supported by positive findings on clastogenicity *in vitro* or *in vivo*. Moreover, it is striking that the number of implantations in the control matings was half the otherwise typical number of implantations for the outbred strain used (only about 6 instead of 13–15 implantations/female). No concurrent positive control was used. The positive findings affect early spermatids and spermatocytes, which are closely connected with Sertoli cells and can develop only in this cell-to-cell contact. Since evidence of damage to Sertoli cells was detected for *p*-phthalic acid, it is assumed that *o*-phthalic acid also leads to such damage, which has negative effects on germ cell development. For these reasons, this isolated positive dominant lethal test cannot be used for the assessment of the germ cell mutagenicity.

A sperm head abnormality assay was carried out in male Swiss albino mice after a single intraperitoneal injection of *o*-phthalic acid doses of 50, 100, 150, 200 and 300 mg/kg body weight with analyses after 1, 3 and 5 weeks. A dose-related, statistically significant increase in abnormal sperm heads was reported after 1 and 3 weeks (Jha *et al.* 1998). A toxic effect, mediated by damaged Sertoli cells, on the development of the spermatids must be assumed here, too. It is unclear whether morphological sperm anomalies have a genetic basis; but if a genetic basis is assumed, the consequences

would have to be obvious in the fifth week after treatment rather than one or three weeks after treatment as described above. This positive finding cannot be used for the assessment of the germ cell mutagenicity of *o*-phthalic acid.

There are no data available for genotoxicity of ***m*-phthalic acid** *in vivo*.

***p*-Phthalic acid**

A positive micronucleus test was obtained in mice after single intraperitoneal injections of *p*-phthalic acid at concentrations of 0.09 to 4.3 mmol/kg body weight (about 15 to 714 mg/kg body weight) and examinations after 24, 48 and 72 hours. There was an increase in micronuclei in polychromatic erythrocytes of the bone marrow, the incidence being highest after 24 hours (Zabrejko and Goncharova 1989). This abstract presented by a Russian working group at a meeting was not published in detail later. Therefore, the study cannot be assessed and is not included in the present review.

A micronucleus test carried out according to OECD Test Guideline 474 was negative with mice 24 or 48 hours after intraperitoneal injection of 200, 400 or 800 mg/kg body weight (BP Amoco 2001).

5.7 Carcinogenicity

There are no data available for ***o*-phthalic acid** or ***m*-phthalic acid**.

***p*-Phthalic acid**

C3H mice were given 0 and 2500 mg *p*-phthalic acid/kg body weight and day in the diet over a period of 12 months. A single mammary tumour was detected in 78% of the control animals and in 50% of the animals exposed; further tumours were not reported (no other details; OECD 2001).

A two-year feeding study with male and female F-344 rats given *p*-phthalic acid doses of 0, 20, 142 or 1000 mg/kg body weight and day revealed, in addition to the non-neoplastic effects (see Section 5.2.2), bladder tumours in 19 of 118 animals of the highest dose group; these were assessed as mainly hyperplasias by a second laboratory. In the females, adenocarcinomas of the uterus in exposed and non-exposed animals were observed as effects not induced by the substance. This was explained by the authors by the fact that a problem with the illumination of the animal rooms was detected 18 months after the beginning of the study. It is not known how long the animals were possibly exposed to a more than 12-hour light phase. Synchronization of the female cycle of rats is regulated by light. If there is continuous illumination, rats remain in the oestrus phase with increased oestrogen levels. It has been demonstrated that oestrogen levels increased for a prolonged period lead to hyperplasias and sometimes also to tumours in the uterus (CIIT 1983a, 1983b).

In a two-year study with male and female Wistar rats, 1%, 2% or 5% *p*-phthalic acid was administered in the diet (corresponding to doses of 500, 1000 or 2500 mg/kg body weight and day for a rat of 400 g with a feed consumption of 20 g/day). The increased

mortality of the animals of the highest dose group is explained by the formation of *p*-phthalic acid stones in the urinary tract and the concurrent occurrence of tumours. The occurrence of stones in the urinary tract led to changes of the epithelium, ranging from hyperplasias, papillomas, metaplasias and carcinomas of the squamous epithelium to tumours of the transitional cells. Bladder stones were observed in the males of the highest dose group in 42/47 animals and in 39/42 of the females. None of the males and 1/48 females in the low dose group had bladder stones and no animal in the middle dose group had bladder stones. Bladder and ureter neoplasms were observed in 21/37 males and 21/34 females in the highest dose group, in 1/48 males and 2/47 females in the middle dose group and in 1/43 males of the lowest dose group. Neoplasms in the urogenital tract were detected in the females of the low dose group and of the control group. Exposure to *p*-phthalic acid did not increase the spontaneous tumour rate; the rate of mammary tumours in the females and carcinomas of the thyroid medulla in the males was reduced (BG Chemie 1990; OECD 2001).

5.8 Other effects

In *in vitro* studies with a cell line from human amniotic tissue, it was demonstrated that *o*-phthalic acid displaces [³H]oestradiol from its binding sites, enhances the intracellular cyclic AMP concentration without influencing the adenylyl cyclase activity and stimulates or inhibits prostaglandin synthesis probably depending on the intracellular nucleotide level. The effect of *o*-phthalic acid on the release of prostanoids can be counteracted by the protein-synthesis inhibitor cycloheximide or by prevention of the diffusion of *o*-phthalic acid through the cell membrane (Pavan *et al.* 2001).

The immunohistochemical examination of proliferating bladder epithelium of male rats with bladder stones after oral *p*-phthalic acid administration revealed an increased expression of proliferating cell nuclear antigen (PCNA), cyclin D1, CDK4 and EGFr, whereas p16Ink4a was deregulated (Dai *et al.* 2005).

6 Manifesto (MAK value/classification)

No studies of humans have been published which would be suitable for deriving a MAK value.

All three isomers are of low acute toxicity in animal studies. The available studies suggest a similar effect of the three isomers. Repeated oral administration led mainly to lesions in the kidneys and urinary tract. After exposure to *p*-phthalic acid doses of at least 1000 mg/kg body weight and day, in particular young mice and rats revealed lesions in the bladder from the second week; these result from crystallization of the substance and some of them develop into tumours of the bladder transitional cells after prolonged exposure. Tumours in the ureter were also observed. The formation of bladder or urinary stones is accompanied by supersaturation of the urine with one of the acids

and precipitation of the substance in the urine as crystals. Calculations showed that this may be the case for *p*-phthalic acid in humans at a daily dose of 2000 mg *p*-phthalic acid and more, assuming 1.5 l urine/day.

Since there are only few data for ***o*-phthalic acid** and no studies with prolonged exposure, this isomer is classified in Section IIb of the *List of MAK and BAT Values*.

***m*-Phthalic acid** is of low acute and systemic toxicity, which leads to lesions from crystallization in the urine only at high doses. There were no effects at concentrations up to 10 mg/m³ in a four-week inhalation study in rats. This difference from *p*-phthalic acid, which had effects on the tracheal epithelium at concentrations of 0.52 mg/m³ and more, might be due to the different solubility in water, which at 130 mg/l for *m*-phthalic acid is higher by a factor of 10 than that for *p*-phthalic acid at 15 mg/l (solubility of *o*-phthalic acid in water: 7010 mg/l at 25°C). In the case of *p*-phthalic acid, particles inhaled and deposited in the trachea might remain there longer until they dissolve and thus cause mechanical irritation for a longer time. They may also have an effect on the epithelium due to their acidity and cause the effects described. Since the inhalation study was carried out only with four-week exposure and the different effect of *m*-phthalic acid and *p*-phthalic acid on the trachea was not substantiated in a second study, the MAK value for *m*-phthalic acid is established at 2 mg/m³. Since the MAK value is established on the basis of local effects, *m*-phthalic acid is classified in Peak limitation category I with an excursion factor of 2.

After four-week exposure of rats to ***p*-phthalic acid**, a dose-dependent degeneration of the tracheal epithelium was observed at concentrations of 0.52 mg/m³ and more. It is surprising that local changes were observed only in the trachea, but not in the nose. Since rats are obligatory nose breathers, at least a partial deposition of particles and resulting epithelial lesions would be expected there. These were not observed. Nor was this effect reported after exposure to *m*-phthalic acid, which may however be due to the different solubility of the two isomers. The alterations in the respiratory epithelium of the trachea are specified in more detail as a reduction of ciliated cells, a certain randomness of the cells in the epithelial lining and occasionally slight hyperplasia of the epithelium. The severity of these alterations does not increase with the exposure concentration although the incidence rises. The degree “minimal” means that there was a very slight deviation from normal, which is only detected by pathologists who are experienced in the area of the respiratory tract. It is conceivable that the sections of *p*-phthalic acid were evaluated by a pathologist experienced in this respect but not those of *m*-phthalic acid. Nevertheless, *p*-phthalic acid caused an alteration that shows a dose-response-specific progression. On the basis of the unchanged systemic parameters (especially haematology and respiratory physiology), the two lower dose levels can be regarded as low effect levels. The lowest dose of 0.52 mg/m³ is therefore used as a basis for establishing a MAK value. Taking into account that the inhalation study only lasted four weeks, the MAK value for *p*-phthalic acid is established at 0.1 mg/m³. Since the MAK value is established on the basis of local effects, *p*-phthalic acid is classified in Peak limitation category I with an excursion factor of 2. Further inhalation studies to confirm or refute the different effect profiles of *m*-phthalic acid and *p*-phthalic acid and that of *o*-phthalic acid would be desirable.

Dermal absorption of *p*-phthalic acid is low. Systemic toxicity is also low. Therefore, *p*-phthalic acid is not designated with an “H”. Since a similar effect of the two other isomers can be assumed, *m*-phthalic acid and *o*-phthalic acid are also not designated with an “H”.

There are no data that would justify a designation of one of the isomers with an “Sa” (sensitizing for the airways) or an “Sh” (sensitizing for the skin).

The available studies have not shown any of the three isomers to be genotoxic. Classification in one of the carcinogenicity categories is therefore not required.

The positive findings obtained for *o*-phthalic acid in the dominant lethal test and in the sperm head abnormality assay carried out by Jha *et al.* (1998) cannot be used for classification in one of the categories for germ cell mutagens on account of methodological inadequacies.

A prenatal toxicity study carried out with ***m*-phthalic acid** and another one carried out with ***p*-phthalic acid** in rats revealed neither maternal toxicity nor prenatal toxicity up to the highest exposure concentrations of 9 and 10 mg/m³, respectively. Although no conclusions can be drawn from either study as to whether toxic effects on development occurred and at what concentrations, these studies show that no prenatal toxicity is expected if the MAK values of 2 and 0.1 mg/m³ are observed. After oral administration of ***o*-phthalic acid**, maternally toxic effects occurred only at doses of 1763 mg/kg body weight and day or more and foetotoxic effects were observed only at 2981 mg/kg body weight and day.

A review of the available data therefore permits the classification of *m*-phthalic acid and *p*-phthalic acid in Pregnancy risk group C. Since it was not possible to derive a MAK value for *o*-phthalic acid, no Pregnancy risk group can be established.

7 References

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