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TOXICOLOGICAL EVALUATIONS

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TOXICOLOGICAL EVALUATION

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Terephthalic acid dimethyl ester

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BG Chemie
Berufsgenossenschaft der chemischen Industrie

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Terephthalic acid dimethyl ester

1 Summary and assessment

Studies of ^{14}C-terephthalic acid dimethyl ester in male Charles-River rats have shown that the chemical is rapidly and almost completely absorbed from the gastrointestinal tract following oral administration. Upon single and repeated semi-occlusive application of ^{14}C-terephthalic acid dimethyl ester to the depilated dorsal skin of rats, recovery of ^{14}C from the urine and faeces was 10.8 and 12.4%, respectively. Absorption was also demonstrated for intratracheal administration to rats and instillation into the conjunctival sac of the rabbit eye. After oral administration of a single dose or the last of multiple doses to male Charles-River rats, respective urinary excretion of ^{14}C-terephthalic acid dimethyl ester was approx. 75 to 86% and approx. 77 to 82% and respective faecal excretion was approx. 4 to 9% and approx. 13 to 16% within 48 hours, independently of the dose of radioactivity administered. Excretion of ^{14}C following intratracheal, dermal and ocular administration also took place predominantly via the kidneys. The exhaled air was not analysed for ^{14}C. The only metabolite of ^{14}C-terephthalic acid dimethyl ester found in the urine of orally treated rats was ^{14}C-terephthalic acid whereas the urine of mice treated in the same manner contained essentially terephthalic acid monomethyl ester. No unchanged ^{14}C-terephthalic acid dimethyl ester was detected in the urine. The faeces of rats dosed orally with ^{14}C-terephthalic acid dimethyl ester were detected to contain traces of unchanged compound, ^{14}C-terephthalic acid monomethyl ester and ^{14}C-terephthalic acid. ^{14}C-Terephthalic acid dimethyl ester and its metabolites do not accumulate in the tissues of the body.

Terephthalic acid dimethyl ester is of low acute toxicity following single oral, inhalation, dermal or even intraperitoneal administration. LD_{50} values determined for oral administration to rats and mice and dermal exposure of guinea pigs are clearly in excess of 2000 mg/kg body weight. Exposure to 6000 mg/m³ or 8-hour exposure to atmosphere enriched or saturated at 20 °C is not lethal to rats. Following intraperitoneal administration, the LD_{50} values for the rat and the mouse range from 1600 to 3650 mg/kg body weight. Single treatment with terephthalic acid dimethyl ester has been found to induce only uncharacteristic, if any, clinical signs of acute toxicity (weakness,

ataxia, tremor, irritation). Necropsy of deceased animals and survivors at study termination yielded no abnormal findings in the majority of cases.

Terephthalic acid dimethyl ester is not irritating to the skin or eyes.

Exploratory skin-sensitisation studies have not yielded any abnormal findings.

Terephthalic acid dimethyl ester is also of low toxicity after repeated administration. The only substance-related, organ-specific effect of terephthalic acid dimethyl ester observed consisted in the induction of calculi in the urinary bladder and subsequent urinary bladder epithelial hyperplasia when the urine saturation points for terephthalic acid and calcium were exceeded following administration of very high quantities of terephthalic acid dimethyl ester. Dose-related formation of urinary bladder stones, the main components of which were terephthalic acid, calcium and protein, was observed to be more pronounced in males, with calculi being noted in male Fischer-344 and Wistar rats after 2 and 13 weeks' administration of feed containing ≥ 1.5% and ≥ 0.5% terephthalic acid dimethyl ester, respectively. Female Fischer-344 and Wistar rats were found to have developed bladder stones after 2 and 13 weeks' dietary administration of terephthalic acid dimethyl ester at and above levels of 2% and 1.6%, respectively. Furthermore, dietary dose levels of terephthalic acid dimethyl ester ≥ 1.5% delayed body weight gain in the Fischer-344 rat in a dose-related manner, reduced urinary pH and phosphate concentration and increased the urinary calcium concentration. According to the investigators' estimate for humans, attainment of the minimum saturating concentration of terephthalic acid in urine requires daily absorption of 2.4 g terephthalic acid dimethyl ester. Dietary administration of 1% terephthalic acid dimethyl ester to male Long-Evans rats over a period of 96 days only resulted in slight, but not statistically significant, reduction in body weight gain at day 91. Body weight at necropsy on study day 96, however, did not differ from the mean control weight. Clinical signs of toxicity, haematology and clinical chemistry findings, kidney and liver weights and histopathological examination of the organs were unremarkable. A subchronic range-finding study for a carcinogenicity study conducted in the context of the US NTP, in which Fischer-344 rats and B6C3F1 mice were administered up to 20000 ppm (2%) in their diets, also only demonstrated depressed body weight gains at and above 10000 ppm in rats. Mortality in mice was 2 out of 10 in the 20000 ppm females while 1 out of 10 males died in each of the groups receiving 2500, 5000 or 20000 ppm. In

the carcinogenicity study itself, dietary administration of terephthalic acid dimethyl ester at levels of up to 5000 ppm over a period of 2 years yielded no abnormal findings in the B6C3F1 mouse or Fischer-344 rat. Also, 58 whole-body exposures to terephthalic acid dimethyl ester dust at levels of 16.5 or 86.4 mg/m³ (4 hours/day, 5 times/week; 36% respirable particles) caused no systemic toxicity in male Long-Evans rats. The animals in the top concentration group, which inhaled terephthalic acid dimethyl ester at an estimated daily dose level of approx. 4 mg/kg body weight according to the investigators, only showed increased nose rubbing, preening and blinking during exposures. The clinical chemistry, haematology, macroscopic and histopathological findings did not differ from those obtained for the control group. It has been reported in the absence of further details that exposure of male Sprague-Dawley rats and male Hartley guinea pigs to terephthalic acid dimethyl ester dust levels of 15 mg/m³ (5 mg respirable dust), 6 hours/day, 5 days/week for 6 months was without abnormal findings. One abstract reports that 5 months' inhalation exposure to terephthalic acid dimethyl ester levels of up to 70 mg/m³ caused systemic and local toxicity in rats. However, lack of experimental data in the available abstract renders it impossible to evaluate the study.

Terephthalic acid dimethyl ester is devoid of genotoxic potential both in vitro and in vivo. The genotoxic effect of terephthalic acid dimethyl ester has been investigated in vitro in Salmonella/microsome tests on *Salmonella typhimurium* strains TA 98, TA 100, TA 102, TA 1535, TA 1537 and TA 1538 and in *Escherichia coli* WP2uvrA, in the L5178Y/TK test on L5178Y mouse lymphoma cells, in micronucleus tests on human lymphocytes, in chromosome aberration tests in Chinese hamster ovary (CHO) cells and human lymphocytes, in the SCE test in CHO cells, UDS tests in HeLa cells and in tests for the induction of DNA single-strand breaks in HeLa cells and SV40-transformed Chinese hamster embryo cells (CO60 cells). The majority of studies, all of which gave negative results, were carried out both in the absence and presence of metabolic activation, in most cases S-9 mix from Aroclor 1254-induced rat livers. In an in-vivo study conducted in compliance with current standards in 1993 in the context of the NTP, terephthalic acid dimethyl ester showed no clastogenic effect in the B6C3F1 mouse micronucleus assay following three intraperitoneal injections of up to 1750 mg/kg body weight. Thus the result of a micronucleus test in (C57Bl/6JxCBA)F1 mice which was evaluated as positive by the investigators in 1988 was not

confirmed. The test involved single intraperitoneal injection of terephthalic acid dimethyl ester at dose levels of up to 194 mg/kg body weight in DMSO as the vehicle, which itself showed toxic effects in this test. There was also no indication of clastogenicity for terephthalic acid dimethyl ester in a chromosome aberration assay performed in accordance with OECD guideline No. 475 in Chinese hamsters given single oral doses of up to 5000 mg/kg body weight. In a study conducted in 1994, terephthalic acid dimethyl ester induced no sex-linked recessive lethal mutations in *Drosophila melanogaster* when administered by feeding or injection. This finding is also in contradiction with a study conducted in 1984 which reported that terephthalic acid dimethyl ester caused dominant lethal mutations in *Drosophila melanogaster*. However, the mortality rates observed in that study were not concentration-dependently or very markedly increased (the increase being only two- to three-fold) and the exact study conduct remains obscure due to imprecise documentation.

In a 2-year carcinogenicity study conducted in the context of the US NTP, in which F344 rats and B6C3F1 mice were treated at dietary levels of up to 5000 ppm, terephthalic acid dimethyl ester was evaluated as not carcinogenic under the conditions of the study.

In a one-generation study, oral administration to Long-Evans rats of terephthalic acid dimethyl ester at levels of up to 1% in the feed did not impair fertility or adversely affect gestation, litter size or postnatal mortality. The only finding was that body weight gain at the 0.5 and 1% levels was retarded in pups at 21 days postpartum. There were no findings at the 0.25% dietary level. When paired, the parental males had been treated with terephthalic acid dimethyl ester for 115 days while the parental females were treated from 6 days before mating until 21 days postpartum. An oral teratogenicity/embryotoxicity study was conducted as a limit test in the Wistar rat in accordance with OECD guideline No. 414. Administration of 1000 mg/kg body weight/day by oral gavage on days 7 to 16 of gestation also gave no indication of any embryotoxic or teratogenic potential for terephthalic acid dimethyl ester. An exploratory embryotoxicity/teratogenicity study showed no embryotoxic or teratogenic effects when albino rats were continuously exposed to terephthalic acid dimethyl ester at 1 mg/m³ throughout pregnancy.

No irritation was caused by either single or repeated dermal applications of an 80-percent oily formulation of terephthalic acid dimethyl ester to the skin

of volunteers. An epidemiological mortality study in workers from a French plant which has been manufacturing, *inter alia*, polyethylene terephthalate fibres since 1956 gave no indication of carcinogenic potential for terephthalic acid dimethyl ester.

In the Federal Republic of Germany, the Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area ("MAK-Kommission") of the Deutsche Forschungsgemeinschaft has listed terephthalic acid dimethyl ester in the "Yellow Pages" of the List of MAK and BAT Values 2004 on the suggestion of BG Chemie in order that a MAK value be established for the chemical.

2 Name of substance

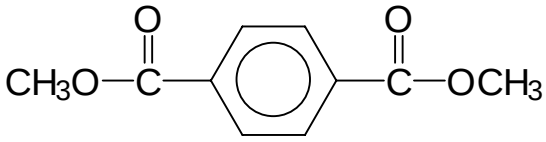
2.1	Usual name	Terephthalic acid dimethyl ester
2.2	IUPAC name	1,4-Benzenedicarboxylic acid dimethyl ester
2.3	CAS No.	120-61-6
2.4	EINECS No.	204-411-8

3 Synonyms, common and trade names

1,4-Benzoldicarbonsäuredimethylester
Benzol-1,4-dicarbonsäure-dimethylester
Dimethyl-1,4-benzenedicarboxylate
p-Dimethylphthalate
Dimethyl-p-phthalat
Dimethyl p-phthalate
Dimethylterephthalat
Dimethyl terephthalate
DMT
Methyl-4-carbomethoxybenzoate
Methyl-p-(methoxycarbonyl)benzoate
Terephthalic acid methyl ester
Terephthalsäuredimethylester

4 Structural and molecular formulae

4.1 Structural formula



4.2 Molecular formula $C_{10}H_{10}O_4$

5 Physical and chemical properties

5.1	Molecular mass, g/mol	194.18	
5.2	Melting point, °C	140.63	(Hoechst, 1978)
		140–141,8	(EC, 2000)
		141	(Falbe and Regitz, 1997)
5.3	Boiling point, °C	282 (at 1013 hPa)	(Creanova, 1998 a, b)
		282–285 (at 1013 hPa)	(EC, 2000)
		284	(Hoechst, 1978)
		288	(Falbe and Regitz, 1997)
		> 400, decomposition	(EC, 2000)
5.4	Vapour pressure, hPa	< 0.02 (at 20 °C)	(EC, 2000)
		< 1 (at 20 °C)	(Creanova, 1998 a, b)
		< 0.13 (at 30 °C)	(EC, 2000)
		1.53 (at 93 °C)	(EC, 2000)
		21 (at 100 °C)	(EC, 2000)
		15.8 (at 140 °C)	(Sheehan, 2001)
		ca. 18 (at 150 °C)	(Hüls, 1994; Creanova, 1998 b)
		26.2 (at 160 °C)	(Sheehan, 2001)
		108.8 (at 200 °C)	(Sheehan, 2001)
		100 (at 208 °C)	(Eastman Kodak, 1986)
		363.8 (at 240 °C)	(EC, 2000)
		426.0 (at 250 °C)	(Sheehan, 2001)
5.5	Density, g/cm³	1.1	(Eastman Kodak, 1986)
		1.35 (at 20 °C)	(Creanova, 1998 a)
		1.075 (at 141 °C)	(Lide and Frederikse, 1997)
		1.084 (at 150 °C)	(Creanova, 1998 b)
		1.04 (at 160 °C)	(Hoechst, 1978)

5.6	Solubility in water	Slightly soluble in hot water (Falbe and Regitz, 1997) 0.029 g/l (at 20 °C) (EC, 2000) 0.036 g/l (at 20 °C) (Creanova, 1998 a, b) 0.5 g/l (at 20 °C) (Hoechst, 1978)
5.7	Solubility in organic solvents	Slightly soluble in hot alcohols, readily soluble in chloroform (Falbe and Regitz, 1997) Benzene: 2.0 and 14.0 g/100 g at 25 and 60 °C, respectively Chloroform: 10.0 and 23.0 g/100 g at 25 and 60 °C, respectively Dioxane: 7.5 and 26.5 g/100 g at 25 and 60 °C, respectively Acetic acid ethyl ester: 3.5 and 16.0 g/100 g at 25 and 60 °C, respectively Methanol: 1.0 and 5.7 g/100 g at 25 and 60 °C, respectively Toluene: 4.3 and 10.4 g/100 g at 25 and 60 °C, respectively (Sheehan, 2001)
5.8	Solubility in fat	Partition coefficient log P_{ow} (measured): 1.66 (EC, 2000) Partition coefficient log P_{ow} (measured at 20 °C): 2.35 (EC, 2000) Partition coefficient log P_{ow} (measured): 2.36 (EC, 2000) Partition coefficient log P_{ow} (measured): 2.4 (Creanova, 1998 a, b)
5.9	pH value	5.9 at 28.7 mg/l (solubility in water at 20 °C) (EC, 2000)
5.10	Conversion factor	1 ml/m³ (ppm) ≙ 8.057 mg/m³ 1 mg/m³ ≙ 0.124 ml/m³ (ppm) (at 1013 hPa and 25 °C)

6 Uses

Terephthalic acid dimethyl ester is mainly used as a starting product for the manufacture of polyester fibres. Further uses are for the manufacture of polyester resins, films, varnishes and adhesives and of poly(ethylene te-

rephthalate) for beverage containers and 1,4-dimethylolcyclohexane (Falbe and Regitz, 1997; Sheehan, 2001).

7 Experimental results

7.1 Toxicokinetics and metabolism

The toxicokinetics of ^{14}C-terephthalic acid dimethyl ester were investigated in male Charles-River rats after single-dose or repeated (5 doses on alternate days) oral, intratracheal or dermal administration and in male New Zealand rabbits after single ocular administration into the conjunctival sac. Depending on the route of administration, 4 to 20 µCi of ring-labelled compound (tracer) and mixtures of unlabelled terephthalic acid dimethyl ester and tracer were administered to groups of 5 animals. Negative controls received the respective vehicle, peanut oil for oral and water containing 1% Triton-X-100 for intratracheal, dermal and ocular administration. Urine and faeces were collected for two 24-hour periods after single oral and intratracheal administration, for 10 days after single dermal and ocular administration and during the period from treatment initiation until 2 days after the final dose following repeated administration. Residual radioactivity levels in the blood, organs and tissues were determined 2 days after the last dose (study day 10) in the substudies with repeated oral, intratracheal or dermal administration and also at study day 10 after single dermal and ocular administration. Excretion of ^{14}C was not measured in the exhaled air. Table 1 shows that the radioactivity administered by single or repeated oral administration of ^{14}C-terephthalic acid dimethyl ester underwent rapid and predominantly urinary excretion, independently of the dose given. Within 24 and 48 hours after single-dose administration, excretion of the administered ^{14}C doses reached 65.4 to 78.7% and 74.9 to 85.9%, respectively. As little as 3.8 to 8.4% of the administered radioactivity was recovered in faeces (total recovery from the urine and faeces was 83.3 to 94.5%). Within 48 hours after the last of 5 oral administrations of the same dose, 77.4 to 82.4% and 12.6 to 16% of the administered radioactivity was eliminated in the urine and faeces, respectively (total excretion being 91.4 to 95%). There was no accumulation in the body. The levels of radioactivity detected in the blood, liver, lungs, heart, kidneys, spleen, adrenal glands, pancreas, testes, brain

and femur at 48 hours after repeated dosing accounted for less than 0.1% of the administered amount of ^{14}C.

Table 1. Distribution and excretion of ^{14}C after single or repeated (5 doses on alternate days) oral administration of ^{14}C-terephthalic acid dimethyl ester to male Charles-River rats (Moffitt et al., 1975)

	Time after single or final dosing (hours)	Cumulative excretion of ^{14}C after administration of tracer (4 µCi ^{14}C-terephthalic acid dimethyl ester per animal and dose) or mixture of unlabelled terephthalic acid dimethyl ester and tracer (% of total radioactivity administered)					
		Single administration			Repeated administration		
		Tracer	40 mg per animal	80 mg per animal	Tracer	40 mg per animal	80 mg per animal
Urine	24	78.7	70.5	65.4	–	–	–
	48	85.9	81.1	74.9	82.4	77.4	79.0
Faeces	24	4.3	2.2	2.9	–	–	–
	48	8.6	3.8	8.4	12.6	14.0	16.0
Blood	48	–	–	–	< 0.1	< 0.1	< 0.1
Tissue[1]	48	–	–	–	< 0.1	< 0.1	< 0.1
Total recovery	24	83.0	72.7	68.3	–	–	–
	48	94.5	84.9	83.3	95.0	91.4	95.0

[1] Analyses were performed for the liver, lungs, heart, kidneys, adrenal glands, spleen, pancreas, testes, brain and bone marrow.
– not determined

Following single intratracheal administration of 6 µCi ^{14}C-terephthalic acid dimethyl ester per animal, recovery of the administered radioactivity in the urine and faeces within 48 hours was 57.5% and 3.2%, respectively. Repeated administration (5 doses in 10 days) did not differ from single-dose administration with regard to urinary or faecal excretion, 53.8% and 2.3% of the administered radioactivity being eliminated in the urine and faeces, respectively, within 48 hours of the last administration. As in repeated oral administration, there was no accumulation of radioactivity in the body after repeated intratracheal administration. At 48 hours after the last administration, a maximum of 0.2% of the total dose of radioactivity administered was detectable in the lungs and tracheal lymph nodes, all other organs and tissues together containing less than 0.1% (see Table 2). The low recovery rates noted after single and repeated intratracheal administration of tracer in combination with 5 or 10 mg terephthalic acid dimethyl ester were attributed by the investigators to experimental problems encountered due to poor solubility and dispersion of the test substance in the aqueous vehicle and/or expulsion of a portion of the dose by the animals upon administration.

Table 2. Distribution and excretion of ^{14}C after single or repeated (5 doses on alternate days) intratracheal administration of ^{14}C-terephthalic acid dimethyl ester to male Charles-River rats (Moffitt et al., 1975)

	Time after single or final dosing (hours)	Cumulative excretion of ^{14}C after administration of tracer (6 µCi ^{14}C-terephthalic acid dimethyl ester per animal and dose) or mixture of unlabelled terephthalic acid dimethyl ester and tracer (% of total radioactivity administered)					
		Single treatment			Repeated treatment		
		Tracer	5 mg per animal	10 mg per animal	Tracer	5 mg per animal	10 mg per animal
Urine	24	51.6	16.2	13.3	–	–	–
	48	57.5	19.1	15.2	53.8	16.7	13.0
Faeces	24	1.8	1.0	0.6	–	–	–
	48	3.2	1.0	1.0	2.3	0.8	1.1
Blood	48	–	–	–	< 0.1	< 0.1	< 0.1
Lung and tracheal lymph nodes	48	–	–	–	0.2	< 0.1	< 0.1
All other tissues[1]	48	–	–	–	< 0.1	< 0.1	< 0.1
Total recovery	24	53.4	17.2	13.9	–	–	–
	48	61.7	20.1	16.2	56.3	17.5	14.1

[1] Analyses were performed for the liver, heart, kidneys, adrenal glands, spleen, pancreas, testes, brain and bone marrow.
– not determined

Upon single semi-occlusive dermal application to the depilated dorsal skin of rats of 80 mg terephthalic acid dimethyl ester together with 4 µCi ^{14}C-terephthalic acid dimethyl ester, 9.3% and 1.5% of the administered dose of radioactivity appeared in the urine and faeces, respectively, within 10 days after dosing. Urinary and faecal recoveries after repeated administration of the same dose (5 doses on alternate days) were 10 and 2.4%, respectively, within 48 hours of the last application (see Table 3). The skin of the application area was detected to contain 5.5 and 3.3% of the administered radioactivity following single and repeated treatment, respectively, while the respective recoveries were 0.8 and 0.2% for the liver and 1.2 and 0.1% for all other organs together (see Table 3). No evidence of skin irritation was noted at the application sites. Single ocular administration of 50 mg terephthalic acid dimethyl ester with an admixture of 20 µCi ^{14}C-terephthalic acid dimethyl ester into the conjunctival sac of one eye also caused no signs of irritation in rabbits. A total of 26.7% of the administered dose of ^{14}C appeared in the urine of animals that had their eyes rinsed with water 5 minutes after instillation, whereas urinary recovery was 35% in animals that did not have their eyes rinsed until 24 hours after dosing. Respective faecal excretion rates were 2.1 and 2.0% of the total amount of radioactivity administered. There was no accumulation in the eyes or other organs (see Table 3).

Table 3. Distribution and excretion of ^{14}C after single or repeated (5 doses on alternate days) semi-occlusive dermal application of ^{14}C-terephthalic acid dimethyl ester to the depilated dorsal skin of male Charles-River rats and after a single 5-minute or 24-hour instillation into the conjunctival sac of male New Zealand rabbits (Moffitt et al., 1975)

	Time after single or final dosing (days)	Cumulative ^{14}C excretion after administration of a mixture of unlabelled terephthalic acid dimethyl ester and 4 µCi (dermal exposure) or 20 µCi (ocular exposure) ^{14}C-terephthalic acid dimethyl ester (% of total radioactivity administered)			
		Dermal application		Ocular administration	
		1 dose of 80 mg per animal	5 doses of 80 mg per animal	1 dose of 50 mg per animal (5 minutes)	1 dose of 50 mg per animal (24 hours)
Urine	10	9.3	10.0	26.7	35.0
Faeces	10	1.5	2.4	2.1	2.0
Application area	10	5.5	3.3	< 0.1	< 0.1
Liver	10	0.8	0.2	no information	no information
All other tissues[1]	10	1.2	0.1	0.1	0.1
Total recovery	10	18.3	16.0	28.9	37.1

[1] Analyses were performed for the liver, heart, kidneys, adrenal glands, spleen, pancreas, testes, brain and bone marrow.

The investigators did not perform a detailed analysis of the metabolites. They only reported that after extraction of the urine with a chloroform-methanol mixture the major portion of radioactivity was found in the aqueous fraction and suspected that terephthalic acid dimethyl ester underwent extensive biotransformation into water-soluble metabolites (Moffitt et al., 1975).

Rats given feed containing 5% terephthalic acid dimethyl ester for 5 days metabolised the absorbed chemical to terephthalic acid and excreted it predominantly in the urine. Only traces of unchanged ester were detectable in the urine. Approximately 15% of the ester ingested with the diet was excreted in the faeces (no further details; Du Pont, 1958).

The only metabolite of ring-labelled ^{14}C-terephthalic acid dimethyl ester (dose not specified) to appear in 24-hour urines after oral administration to 3 male F344 rats was ^{14}C-terephthalic acid. No unchanged ^{14}C-terephthalic acid dimethyl ester or ^{14}C-terephthalic acid monomethyl ester was detected in the urine. The faeces, which were also collected for 24 hours, were analysed to contain traces of ^{14}C-terephthalic acid, ^{14}C-terephthalic acid monomethyl ester and ^{14}C-terephthalic acid dimethyl ester (Heck and Kluwe, 1980).

In contrast to rats, where metabolism of terephthalic acid dimethyl ester almost exclusively yielded terephthalic acid (see above; Heck and Kluwe, 1980), B6C3F1 mice metabolised ^{14}C-terephthalic acid dimethyl ester to ^{14}C-terephthalic acid monomethyl ester under comparable experimental conditions (no further details; Heck and Tyl, 1985).

7.2 Acute and subacute toxicity

Acute toxicity

The acute toxicity data for terephthalic acid dimethyl ester are summarised in Table 4 below. Terephthalic acid dimethyl ester was of low acute toxicity following oral, inhalation, dermal or intraperitoneal administration. LD_{50} values determined for oral administration to rats and mice and dermal exposure of guinea pigs were clearly in excess of 2000 mg/kg body weight (see Table 4). Exposure to 6000 mg/m³ or 8-hour exposure to atmosphere enriched or saturated at 20 °C was not lethal to rats (see Table 4; Sanina and Kochetkova, 1963; BASF, 1961). Following intraperitoneal administration, the LD_{50} values ascertained for the rat and the mouse were in the range from 1600 to 3650 mg/kg body weight (see Table 4). A single treatment with terephthalic acid dimethyl ester induced only unspecific, if any, clinical signs (weakness, ataxia, tremor, signs of irritation) and necropsy findings were unremarkable in the majority of animals that died intercurrently or were sacrificed at study termination (see Table 4). However, peritoneal irritation was noted at necropsy after intraperitoneal administration (Krasavage et al., 1973).

Beginning of Table 4

Table 4. Acute toxicity studies of terephthalic acid dimethyl ester

Species, strain, sex[1]	Route	Dose (mg/kg body weight or mg/m³)	Purity	Effect	Observation period	Reference
Rat, albino	oral	2000	n. d.	not lethal	n. d.	Prusakov, 1966
Rat	oral	> 3200	n. d.	LD_{50}	n. d.	Eastman Kodak, not dated
Rat, albino, male	oral	4600, administered as a 15% suspension in olive oil	n. d.	mortality: 0/9	28 days	Massmann, 1966

Table 4. Acute toxicity studies of terephthalic acid dimethyl ester						
Species, strain, sex[1]	Route	Dose (mg/kg body weight or mg/m³)	Purity	Effect	Observation period	Reference
Rat, Long Evans, male	oral	6590; dose range tested: 3000–6590, administered as a 20% formulation in corn oil	technical grade	mortality: 0/3 or 0/6 (equivocal data); weakness, ataxia, tremors; necropsy and histopathological examination without abnormal findings	14 days	Krasavage et al., 1973
Rat	oral	> 10000, administered as a 30% suspension in tragacanth gum	n. d.	LD_{50}; no characteristic clinical signs (no further details)	7 days	BASF, 1961
Rat	oral	14400	n. d.	LD_{50}	n. d.	Nishimura et al., 1994
Mouse	oral	> 3200	n. d.	LD_{50}	n. d.	Eastman Chemical Products, 1976
Mouse	oral	10000	n. d.	not lethal, increased excitability	n. d.	Sanina and Kochetkova, 1963
Chinese hamster, male, female	oral	5000	> 99%	mortality: 0/8; no clinical signs	n. d.	CCR, 1990
Rat	inhalation	6000; concentration range tested: 1000–6000	n. d.	not lethal; excitation, hyperaemia of the mucous membranes, erythrocytopenia, hypohaemoglobinaemia, increased threshold of neural excitability (no further details)	n. d.	Sanina and Kochetkova, 1963
Rat	inhalation	atmosphere enriched or saturated at 20 °C, 8 hours	n. d.	mortality: 0/6; no clinical signs of toxicity; no remarkable necropsy findings	n. d.	BASF, 1961
Guinea pig	dermal	> 5000	n. d.	LD_{50}	n. d.	Eastman Kodak, not dated
Rat	intraperitoneal	> 3200	n. d.	LD_{50}	n. d.	Eastman Kodak, not dated
Rat, albino, male	intraperitoneal	3650; dose range tested: 2200–5000, administered as a 15% suspension in olive oil	n. d.	LD_{50}; death 8 to 42 hours after dosing, lateral position; no remarkable necropsy findings	28 days	Massmann, 1966
Rat, Long Evans, male	intraperitoneal	3900; dose range tested: 3000–6590, administered as a 20% formulation in corn oil	technical grade	LD_{50}; weakness, ataxia and tremors; necropsy and histopathological examination revealed no abnormalities except peritoneal irritation	14 days	Krasavage et al., 1973

Table 4. Acute toxicity studies of terephthalic acid dimethyl ester						
Species, strain, sex[1]	Route	Dose (mg/kg body weight or mg/m³)	Purity	Effect	Observation period	Reference
Rat	intraperitoneal	4500	n. d.	LD_{100}	n. d.	Slyusar and Cherkasov, 1964
Mouse	intraperitoneal	1600–3200	n. d.	LD_{50}	n. d.	Eastman Chemical Products, 1976
Mouse	intraperitoneal	> 3200, administered as a 30% suspension in tragacanth gum	n. d.	LD_{50}; no characteristic clinical signs (no further details)	24 hours	BASF, 1961
Mouse	intraperitoneal	3000, administered as a 30% suspension in tragacanth gum	n. d.	LD_{50}; no characteristic clinical signs (no further details)	7 days	BASF, 1961
No information	no information	14400 (12500–16700)	n. d.	LD_{50}	n. d.	Marhold, 1972

[1] where specified
n. d. no data

End of Table 4

Subacute toxicity

Administration of terephthalic acid dimethyl ester at 3750 mg/kg body weight (5% in the feed) for 28 days resulted in weight loss, decreased food consumption and high mortality in rats. There were no haematological changes (no further details; Eastman Kodak, year not specified).

With a focus solely on changes in the kidney and urinary tract, urine composition, body weight gain and food and water consumption, young male and female Fischer-344 rats were examined after 2 weeks' treatment from the age of 28 days with a diet containing 0 (control), 0.5, 1, 1.5, 2 or 3% terephthalic acid dimethyl ester (high purity, no further details). Average dietary intake of terephthalic acid dimethyl ester in the three higher dose groups was 1.89, 2.26 and 2.59 g/kg body weight/day for males and 1.79, 2.29 and 3.02 g/kg body weight/day for females (no details given for the two lower dose groups). Concentration levels ≥ 1.5% resulted in lower rates of body weight gain corresponding to reduced food intake. The quantities of water consumed by animals treated with terephthalic acid dimethyl ester were comparable to controls. According to a graphic representation of the findings, approx. 32, 71 and 100% of males in the three highest dose groups and 33 and 45% of females in the two highest dose groups develo-

ped urinary bladder stones. These essentially consisted of terephthalic acid, calcium and protein. All animals with bladder calculi exhibited urinary bladder epithelial hyperplasia, some also showing hydronephrosis. Haematuria was frequently observed in the highest dose group. Urinary pH was lowered and urinary calcium concentrations were elevated in the dose groups which developed bladder stones. Urinary phosphate levels were reduced in males in the top dose group and in females in the three highest dose groups. Later studies showed that the urinary concentration of ammonium was increased while the urinary concentrations of potassium and sulphate were decreased at the dose levels mentioned, the concentration of urinary sodium remaining unchanged (Heck and Kluwe, 1980; Heck and Tyl, 1985). The urinary concentrations of terephthalic acid observed in the three highest dose groups were 46 ± 9, 105 ± 16 and 106 ± 13 mM for males and 23 ± 7, 116 ± 20 and 127 ± 16 mM for females. The investigators considered high supersaturation of the urine with terephthalic acid and calcium (ordinary saturation concentration for terephthalic acid being 11 to 22 mM, depending on ionic strength and composition of the rat urine) to be the cause of bladder calculus formation and subsequent urinary bladder epithelial hyperplasia. According to their estimate for humans, attainment of the minimum saturating concentration of terephthalic acid in urine requires daily absorption of 2.4 g terephthalic acid dimethyl ester (Chin et al., 1981; Heck, 1981, 1987; Heck and Tyl, 1985).

Oral administration by gavage of terephthalic acid dimethyl ester at 5000 mg/kg body weight 5 times per week for 2 weeks resulted in progressive weight loss in rats. Five out of 6 rats died by study day 11. The pathology findings were suggestive of starvation (no further details; Du Pont, not dated, a).

Piglets (aged 2 to 4 months, 5 piglets/group) were administered terephthalic acid dimethyl ester at dose levels of 0 (control), 26, 260 or up to 10000 mg/kg body weight in their feed for 30 days (no further details; the highest dose corresponded to 3% in feed). Treatment gave rise to restlessness, atypical behaviour, diarrhoea, coughing and depressed weight gain at the two highest dose levels. Variability was noted in white blood cell counts and the levels of albumin and immunoglobulins. Necropsy revealed gastroenteritis and changes in the bronchi, liver and kidneys. Cooked meat from animals treated at high dose levels had a specific aftertaste and was not normal in colour. Thin-layer chromatography revealed that the stomach, in-

testine, muscle tissue, liver, kidney and skin contained traces of terephthalic acid dimethyl ester at the two highest dose levels. Further groups of 10 animals were exposed to terephthalic acid dimethyl ester at 0.1, 10 or 100 mg/m³, presumably for 30 days, 24 hours/day (no clear details; it is also possible, however, that they were exposed for only one day and then kept under observation for 30 days). The animals in the two higher dose groups alternately showed restlessness and lethargy, coughed more and exhibited slightly elevated body temperature. Leukocytes and immunoglobulins were increased, haemoglobin was decreased and morphological changes were observed in the lung and liver. As in the oral study, the meat had an unusual taste and contained traces of terephthalic acid dimethyl ester (Zhuk and Karput, 1986). The study is unsuitable for evaluating the toxicological potential of terephthalic acid dimethyl ester on account of serious flaws in study conduct and documentation (unclear study design, no analytical verification, etc.).

7.3 Skin and mucous membrane effects

An acute dermal irritation test carried out in accordance with US EPA guidelines found terephthalic acid dimethyl ester to be nonirritant. A 4-hour semi-occlusive application of 500 mg terephthalic acid dimethyl ester, moistened with water, to the depilated intact dorsal skin of each of 6 male New Zealand rabbits produced no signs of skin irritation during the observation period of 24 hours (Safepharm, 1989).

The acute skin irritancy of terephthalic acid dimethyl ester was studied in rabbits by applying a 50-percent aqueous formulation of the chemical to the dorsal skin for 1, 5 or 15 minutes or 20 hours, or to the skin of the ear for 20 hours. No signs of irritation were observed during the subsequent observation period of 8 days (no further details; BASF, 1961). Terephthalic acid dimethyl ester was not irritating to the skin according to these results.

Terephthalic acid dimethyl ester caused no irritation when 80 mg in 0.2 ml distilled water was applied semi-occlusively to the depilated skin of male Charles-River rats once or 5 times within 10 days (duration of exposure not specified; Moffitt et al., 1975).

At 5000 mg/kg body weight, terephthalic acid dimethyl ester (moistened with distilled water) induced only mild dermal irritation when applied to the

guinea pig skin under occlusive cover for 24 hours (Eastman Chemical Products, 1976).

Repeated dermal exposure of rabbits and mice to terephthalic acid dimethyl ester reportedly involved dermatitis and pigmentation (no further details; Sanina and Kochetkova, 1963).

The eyes of rabbits exhibited barely perceptible reddening one hour after introduction into the conjunctival sac of 50 mm^3 of terephthalic acid dimethyl ester, ground to a powder. The animals were normal 24 hours and 8 days after administration (BASF, 1961). Terephthalic acid dimethyl ester was not irritating to the eye according to these results.

In the context of a toxicokinetics study (see Section 7.1; Moffitt et al., 1975), 8 male New Zealand rabbits each had 50 mg terephthalic acid dimethyl ester (containing 20 µCi ^{14}C-terephthalic acid dimethyl ester) instilled into the conjunctival sac of one eye. The eyes of 5 and 3 animals were washed with water after 5 minutes and 24 hours, respectively. No signs of irritation were observed during the subsequent observation period of 10 days (no further details; Moffitt et al., 1975).

A 15-percent oily solution of terephthalic acid dimethyl ester caused no irritation to the mucous membranes of the rabbit eye (no further details; Massmann, 1966).

In the absence of further details, one report claims that terephthalic acid dimethyl ester is mildly irritating to the eye but not irritating to the skin (Marhold, 1972).

Application of 2 drops of a 5-percent formulation of terephthalic acid dimethyl ester in starch reportedly caused mucous membrane irritation in the rabbit eye (no further details; Sanina and Kochetkova, 1963).

7.4 Sensitisation

Studies conducted to assess the skin-sensitising potential of terephthalic acid dimethyl ester in the guinea pig by means of the “drop-on” and “footpad” techniques gave no indication that the chemical was a sensitiser. Groups of 10 animals received four 0.5 ml applications of a 1-percent solution of terephthalic acid dimethyl ester in a mixture of acetone, dioxane and

guinea pig fat (7 : 2 : 1) to the skin of the rump area within one week. One group was challenged by applying 0.5 ml of the formulation to the skin of the shoulder after a treatment-free period of 3 weeks. The other group underwent further induction one week after receiving four dermal applications. This was accomplished by injecting a footpad with a mixture of the terephthalic acid dimethyl ester formulation with whole heparinised rabbit blood. In the second group, dermal challenge with 0.5 ml of the terephthalic acid dimethyl ester formulation one week later gave negative readings at 24 and 48 hours. The same results were obtained for the first group which received only dermal treatment (Krasavage et al., 1973).

7.5 Subchronic and chronic toxicity

In a range-finding study for a carcinogenicity study conducted in the context of the US NTP (see Section 7.7; NCI, 1979), groups of 10 Fischer-344 rats and 10 B6C3F1 mice per sex and dose were fed a diet containing 1750, 2500, 5000, 10000 or 20000 ppm terephthalic acid dimethyl ester for 13 weeks. The controls were fed diet containing the vehicle, corn oil (2%). Treatment with terephthalic acid dimethyl ester did not affect the animals in terms of appearance, behaviour or food consumption. All rats survived. Death occurred in 2 female mice in the 20000 ppm group and in one male mouse per group in the 2500, 5000 and 20000 ppm dose groups. The rats in the two highest dose groups showed slightly depressed body weight gain. Relative to the controls, the respective terminal body weights for the 10000 and 20000 ppm groups were 90 and 83% in males and 83 and 71% in females. Apart from diffuse hepatocyte hypertrophy, which was independent of dose and present in both in rats and mice of all dose groups, there were no pathological findings at macroscopic or histological examination (no further details; NCI, 1979).

Groups of 30 male Long-Evans rats were fed a diet containing 0 (control), 0.25, 0.5 or 1% terephthalic acid dimethyl ester in a subchronic oral study. According to the investigators, this was equivalent to doses of approx. 50 to 200 mg/animal/day. Terephthalic acid dimethyl ester (purity unspecified) was mixed with corn oil and chloroform under heating and added to the feed. The chloroform was subsequently allowed to evaporate by spreading the diets out on trays. The corn oil content of the diet formulations was 2%. The investigators provided no data on residual chloroform content. Haema-

tology (haematocrit, haemoglobin, white cell and differential counts) and clinical chemistry determinations (aspartate aminotransferase, alkaline phosphatase, ornithine carbamoyl transferase, blood urea nitrogen, blood glucose, serum protein) were performed on days 55 and 90. After 96 days of continued dietary administration, 10 animals/group were sacrificed and examined for gross pathology and histopathology. The remaining 20 animals/group continued treatment with terephthalic acid dimethyl ester until study day 115, at which time they were paired, under continued dietary administration, with females which had received identical doses for the previous 6 days (see Section 7.8; Krasavage et al., 1973). After mating, the males discontinued treatment with terephthalic acid dimethyl ester and were placed under observation for one year. The only substance-related effect seen was a statistically significant ($p < 0.05$) reduction in weight gain in the highest dose group (fed a diet containing 1 percent terephthalic acid dimethyl ester) relative to control on study day 91. The animals treated with terephthalic acid dimethyl ester were without clinical findings and their food consumption was comparable with controls. Haematology and clinical chemistry parameters showed no pathological changes. Average body and relative and absolute kidney and liver weights did not differ from control weights at necropsy on study day 96. Histological examination of all organs (no further details) revealed no substance-related pathological findings. One year after discontinuation of treatment, recovery groups showed no clinical signs, and haematology, clinical chemistry and histopathology examinations in a number of sacrificed animals were without abnormal findings (Krasavage et al., 1973).

Male and female Wistar rats (28 days old at the beginning of administration; respective initial body weights 56 and 55 g) were given terephthalic acid dimethyl ester at dietary concentration levels of 0.5, 1.6 and 3.0% for 13 weeks. Treatment caused urinary bladder calculi in 12 out of 16 males and 6 out of 16 females in the high dose group, in 1 out of 19 males in the intermediate dose group and in 2 out of 19 males in the low dose group. Moderate hyperplasia of the bladder urothelium was diagnosed in 11 out of 16 male rats and 7 out of 16 females in the 3% group. A strong correlation was found between the presence of uroliths and the development of hyperplasia of the bladder urothelium. No other pathological changes were observed (no further details; Vogin, 1972).

Increased irritability was observed in 2 out of 4 dogs after oral administration of terephthalic acid dimethyl ester at 100 mg/kg body weight/day for 40 days or 200 mg/kg body weight/day for 62 days. Blood pressure was reduced in 3 out of 4 dogs. No gross or microscopic pathological changes were noted (no further details; Du Pont, not dated, b).

In a subchronic inhalation study, groups of 30 male Long-Evans rats underwent a total of 58 whole-body exposures to terephthalic acid dimethyl ester at analytically determined concentrations of 0 (control), 16.5 or 86.4 mg/m³ for 4 hours/day, except on weekends and public holidays. They were exposed to terephthalic acid dimethyl ester dust (purity unspecified) containing particles with a median aerodynamic diameter of 6.6 µm; 36% of particles were ≤ 5 µm in diameter and respirable. The investigators estimated that the daily doses of terephthalic acid dimethyl ester inhaled by the animals were 0 (control), 0.7, 368 or 4.0 mg/kg body weight. The scope of investigation corresponded to the scope of the feeding study described above, which was conducted in parallel and, as in that study, the animals were placed under observation for one year after the end of the exposure period. As with oral administration, inhalation of terephthalic acid dimethyl ester was largely without abnormal findings. The only treatment-related effects were nose rubbing, preening and blinking, which were observed in animals of the top dose group during inhalation exposure. The clinical observations and haematology, clinical chemistry, macroscopic and histopathological findings did not differ from those obtained for the control group. Animals placed under observation for one year also showed no remarkable findings (Krasavage et al., 1973).

In a further inhalation study, adult male Sprague-Dawley rats and male Hartley guinea pigs were exposed to terephthalic acid dimethyl ester dust at a concentration level of 15 mg/m³ for 6 hours per day on 5 days per week for 6 months. The level of respirable dust was 5 mg/m³. Exposure to terephthalic acid dimethyl ester showed no abnormalities in either species. Body weights, relative and absolute lung, liver, kidney and spleen weights as well as clinical chemistry (SMA 12 screen) and urinalysis parameters all remained unchanged compared with the control. Gross and histopathological evaluations were within normal limits (no further details; Lewis et al., 1982).

Exposure of rats to terephthalic acid dimethyl ester at levels of 1 to 4 mg/m³ for 2 hours/day over a period of 5 months (aerosol or vapours, no further details) caused conjunctivitis, hypodynamia, decrease in blood pressure, erythrocytopenia, leukopenia, reticulocytosis and increased neuroexcitability. Exposure to levels of 40 to 70 mg/m³, 2 hours/day for 5 months, resulted in death in 30% of exposed rats after 2.5 to 3 months and caused depilation, rhinitis, decrease in hippuric acid formation and in some cases cataracts. Necropsy revealed signs of inflammation the respiratory tract (tracheobronchitis), haemorrhage in the lungs, brain and myocardium as well as dystrophic changes in the liver and kidneys (no further details; Sanina and Kochetkova, 1963). Lack of experimental data in the available abstract renders it impossible to evaluate the study.

Ten female albino rats with initial and terminal body weights of approx. 125 g and 214 g, respectively, were intraperitoneally injected with a 15-percent suspension of terephthalic acid dimethyl ester in olive oil (5 times 1.0 ml, 10 times 1.5 ml and 2 times 1.7 ml/rat, the total dose amounting to 3.5 g/rat) once a week over a period of 109 days. The animals appeared normal throughout the study period. Body weights were depressed from study week 6 relative to controls treated with olive oil. One rat died after 56 days. Necropsy revealed no pathological findings (no further details; Massmann, 1966).

7.6 Genotoxicity

7.6.1 In vitro

The in-vitro tests performed to assess the genotoxicity of terephthalic acid dimethyl ester are summarised in Table 5 below. The majority of studies gave no indications that terephthalic acid dimethyl ester was mutagenic or caused chromosome or DNA damage either in the presence or in the absence of metabolic activation; all test results were negative. Mutagenicity was assessed in numerous Salmonella/microsome assays, which were carried out as standard plate incorporation tests, preincubation tests or spot tests using *Salmonella typhimurium* strains TA 98, TA 100, TA 102, TA 1535, TA 1537 and TA 1538, and in *Escherichia coli* WP2uvrA and in the L5178Y/TK test in L5178Y mouse lymphoma cells in the absence and presence of metabolic activation (S9-Mix from Aroclor 1254-induced rat or

Syrian hamster livers or sodium phenobarbitone- or 5,6-benzoflavone-induced livers of male Sprague-Dawley rats). The available data on the chromosome-damaging potential of terephthalic acid dimethyl ester were obtained from in-vitro micronucleus tests in human lymphocytes and chromosome aberration tests in Chinese hamster ovary (CHO) cells and human lymphocytes. With regard to DNA-damaging effects, there are results from an SCE test in CHO cells, from UDS tests in HeLa cells and from tests measuring the induction of DNA single-strand breaks in HeLa cells and SV40-transformed Chinese hamster embryo cells (CO60 cells). The majority of the studies were carried out in both the absence and the presence of S-9 mix from Aroclor 1254-induced rat livers.

Beginning of Table 5

Table 5. In-vitro genotoxicity tests with terephthalic acid dimethyl ester

Test system	Concentration range tested	Purity, vehicle (positive controls)[1]	Metabolic activation system[1]	Result		Reference
				with metabolic activation	without metabolic activation	
1 Gene mutation						
Salmonella/microsome assay, performed as a standard plate incorporation test; TA 98, TA 100, TA 102, TA 1535, TA 1537, TA 1538	0 (negative control), bacteriotoxic at 0.5 to 5000 µg/plate (5000 µg/plate in TA 98 (– S9 mix) and TA 1537 (+ S9 mix))	technical grade; DMSO and Tween 20 in a 29 : 1 ratio	S9 mix	negative	negative	Monarca et al., 1991
Salmonella/microsome assay, performed as a standard plate incorporation test; TA 98, TA 100, TA 1535, TA 1537, TA 1538	0 (negative control), 0.5 up to 5000 µg/plate	purity unspecified; 3% DMSO and 1% Tween 20 (2-nitrofluorene, 9-aminoacridine, sodium azide, 2-aminoanthracene)	S9 mix from Aroclor 1254-induced male Sprague-Dawley rat livers	negative	negative	Lerda, 1996, 1998
Salmonella/microsome assay, performed as a standard plate incorporation test; TA 98, TA 100	up to 1000 µg/plate	no information	S9 mix from Aroclor 1254-induced male Sprague-Dawley rat livers	negative	negative	Kozumbo et al., 1982
Salmonella/microsome assay as a standard plate incorporation test	up to 10000 µg/plate	no information	S9 mix	negative	negative	Du Pont, 1979
Salmonella/microsome assay, performed as a preincubation test; TA 98, TA 100, TA 1535, TA 1537; test with independent repeat	0 (negative control), bacteriotoxic at 33 to 333 µg/plate (333 µg/plate was the highest soluble concentration)	99%; DMSO (4-nitro-p-phenylenediamine, sodium azide and 2-aminoanthracene)	S9 mix from Aroclor 1254-induced livers of male Sprague-Dawley rats and male Syrian hamsters	negative	negative	Zeiger et al., 1982, 1985
Salmonella/microsome assay, performed as a preincubation test; TA 98, TA 100, TA 1535, TA 1537, TA 1538 and parallel testing in *Escherichia coli* WP2uvrA (pKM101); test in accordance with the Japanese guidelines	0 (negative control), 20 up to 5000 µg/plate	purity: guaranteed reagent; DMSO (2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide, 2-aminoanthracene, sodium azide, 9-aminoacridine, 2-nitrofluorene)	S9 mix from phenobarbitone sodium and 5,6-benzoflavone-induced male Sprague-Dawley rat livers	negative	negative	JETOC, 1996

Table 5. In-vitro genotoxicity tests with terephthalic acid dimethyl ester						
Test system	Concentration range tested	Purity, vehicle (positive controls)[1]	Metabolic activation system[1]	Result		Reference
				with metabolic activation	without metabolic activation	
Salmonella/microsome assay, performed as a spot test; TA 98, TA 100, TA 1535, TA 1537, TA 1538; test in accordance with Directive 84/449/EEC B.14 with independent repeat	applied as the undiluted substance; bacteriotoxicity tested	99.99% (nitrofluorene, sodium azide, aminoacridine)	S9 mix from Aroclor- or phenobarbitone-induced rat liver	negative	negative	Hüls, 1993
L5178Y/TK assay, trifluorothymidine resistance assay, L5178Y/TK mouse lymphoma cells, clone 3.7.2C; assay with independent repeat, 3 cultures/concentration	0 (negative control), 6.25 up to 100 µg/ml (solubility limit was exceeded at 75 µg/ml; relative total growth was 94 to 118% without S9 mix and 68 to 75% with S9 mix at the highest soluble concentration of 50 µg/ml)	purity unspecified; dimethyl formamide (methyl methanesulphonate, 3-methylcholanthrene)	S9 mix from Aroclor 1254-induced male Fischer-344 rat livers	negative	negative	Myhr and Caspary, 1991; Tennant et al., 1987
2 Chromosome damage						
Micronucleus test; human lymphocytes from the peripheral blood of two donors (22 and 25 years of age), test with independent repeat and analysis of 2 x 1000 cells/culture	0 (negative control), 0.5 up to 500 µg/ml	purity unspecified; 1% DMSO (bleomycin)	S9 mix from Aroclor 1254-induced male Sprague-Dawley rat livers	negative	negative	Lerda, 1996, 1998
Micronucleus test; human lymphocytes from the peripheral blood of two donors (25 and 28 years of age), 2 x 1000 cells/culture scored	0 (negative control), 50 up to 500 µg/ml	technical grade; DMSO and Tween 20 in a 29 : 1 ratio (bleomycin)	not tested	not tested	negative	Monarca et al., 1991
Chromosome aberration test; Chinese hamster ovary (CHO) cells, 100 cells/culture scored	0 (negative control), 1 up to 10 µg/ml	99%; DMSO (mitomycin C, cyclophosphamide)	S9 mix from Aroclor 1254-induced male Sprague-Dawley rat livers	negative	negative	Loveday et al., 1990

Table 5. In-vitro genotoxicity tests with terephthalic acid dimethyl ester						
Test system	Concentration range tested	Purity, vehicle (positive controls)[1]	Metabolic activation system[1]	Result		Reference
				with metabolic activation	without metabolic activation	
Chromosome aberration test; human lymphocytes from the peripheral blood of two donors (25 and 28 years of age), 2 x 100 cells/culture scored	0 (negative control), 50 up to 500 µg/ml	technical grade; DMSO and Tween 20 in a 29 : 1 ratio (bleomycin)	not tested	not tested	negative	Monarca et al., 1991
3 DNA damage						
SCE test; Chinese hamster ovary (CHO) cells	0 (negative control), 1 up to 10 µg/ml	99%; DMSO (mitomycin C, cyclophosphamide)	S9 mix from Aroclor 1254-induced male Sprague-Dawley rat livers	negative	negative	Loveday et al., 1990
DNA single-strand breaks, primary rat hepatocytes, alkaline elution, test with independent repeat	0 (negative control), 3.75 up to 15 µg/tube	technical grade; DMSO and Tween 20 in a 29 : 1 ratio (N-nitrosomethylbenzylamine)	not tested	not tested	negative	Monarca et al., 1991
DNA single-strand breaks, SV40-transformed Chinese hamster embryo cells (CO60 cells), alkaline elution	0 (negative control), 3.75 up to 15 µg/tube	technical grade; DMSO and Tween 20 in a 29 : 1 ratio (N-nitrosomethylbenzylamine)	not tested	not tested	negative	Monarca et al., 1991
UDS test; HeLa cells (heteroploid human cells), measurement of DNA repair synthesis by scintillation counting of ^{3}H-TdR incorporation into the acid-insoluble DNA fraction in the absence and presence of hydroxyurea as an inhibitor of semiconservative DNA replication; test with an independent repeat	0 (negative control), 0.5 up to 500 µg/ml	purity unspecified; 3% DMSO and 1% Tween 20 (ethyl methanesulphonate, 2-aminoanthracene)	S9 mix from Aroclor 1254-induced male Sprague-Dawley rat livers	negative	negative	Lerda, 1996, 1998

Table 5. In-vitro genotoxicity tests with terephthalic acid dimethyl ester

Test system	Concentration range tested	Purity, vehicle (positive controls)[1]	Metabolic activation system[1]	Result		Reference
				with metabolic activation	without metabolic activation	
UDS test; HeLa cells (heteroploid human cells), measurement of DNA repair synthesis by scintillation counting of ^{3}H-TdR incorporation into the acid-insoluble DNA fraction in the absence and presence of hydroxyurea as an inhibitor of semiconservative DNA replication	0 (negative control), 0.5 up to 5000 µg/ml	technical grade; DMSO and Tween 20 in a 29 : 1 ratio (ethyl methanesulphonate, N-methyl-N'-nitro-N-nitrosoguanidine)	S9 mix from Aroclor 1254-induced Sprague-Dawley rat livers	negative	negative	Monarca et al., 1991
4 Other tests						
Selective DNA amplification; Syrian hamster embryo cells infected with AAV2 (adeno-associated virus)	0 (negative control), 0.5 up to 10 µg/ml	technical grade; DMSO and Tween 20 in a 29 : 1 ratio (1,12-dimethylbenzanthracene, mitomycin C, daunomycin)	not tested	not tested	negative	Monarca et al., 1991

[1] where specified
^{3}H-TdR tritium-labelled methylthymidine
DMSO dimethyl sulphoxide

End of Table 5

7.6.2 In vivo

In a micronucleus test performed on (C57Bl/6JxCBA)F1 mice, 15 males per group received a single intraperitoneal injection of terephthalic acid dimethyl ester at dose levels of 0.20, 0.25, 0.33, 0.50 or 1.00 mmol/kg body weight (approx. 39, 49, 64, 97 or 194 mg/kg body weight). Negative controls were treated with water or the vehicle DMSO, while positive controls received methyl nitrosourea. The volume administered was 0.2 ml/animal. No higher dose levels could be tested due to vehicle toxicity, according the investigators. Twenty-one animals died out of a total of 270 treated with DMSO and/or terephthalic acid dimethyl ester. As the deceased animals were randomly distributed across all dose groups, the investigators attributed the deaths to toxicity on the part of the vehicle used, DMSO. Erythrocytes obtained from each of 6 to 12 animals/group at 24, 48 and 72 hours after administration were analysed for percentage of polychromatic erythrocytes in 200 erythrocytes/animal, and 1000 polychromatic erythrocytes/animal were scored for the presence of micronuclei. The rates of micronuclei showed significant dose-related increases in all dose groups at 24 hours after administration and in dose groups treated at > 0.25 and > 0.33 mmol/kg body weight at 48 and 72 hours after administration, respectively. The highest test dose had a cytotoxic effect on bone marrow. In this dose group, the percentage of polychromatic erythrocytes at 24 hours after administration was 36.91% and thus lower than in the water (40.97%) or DMSO (43.27%) treated controls (Goncharova et al., 1988). The investigators evaluated the result as positive. However, the value of the study is greatly limited by the fact that the vehicle used, DMSO, exhibited toxic effects.

By contrast, no genotoxicity was observed in a further micronucleus assay performed by US federal agencies in the context of the NTP, in which male B6C3F1 mice were treated intraperitoneally for 3 consecutive days with terephthalic acid dimethyl ester at dose levels of 0 (negative control), 438, 875 or 1750 mg/kg body weight, formulated in corn oil. The highest test dose of 1750 mg/kg body weight represented the maximum amount able to be formulated for administration in a volume of 0.4 ml corn oil per animal. The dose was not lethal, caused no change in the percentage of polychromatic erythrocytes in the bone marrow and did not result in any increase in the frequency of micronucleated polychromatic erythrocytes in the bone marrow. The bone marrow from 5 or 6 animals/dose was isolated 24 hours after the last administration. The percentage of polychromatic erythrocytes

was determined in 200 erythrocytes/animal, and 2000 polychromatic erythrocytes/animal were scored for the presence of micronuclei. Positive controls treated with 7,12-dimethylbenzanthracene or mitomycin C exhibited the expected increases in micronucleus frequency (Shelby et al., 1993).

Terephthalic acid dimethyl ester (> 99% pure) was also devoid of clastogenicity in a chromosome aberration assay in Chinese hamsters given single oral doses of up to 5000 mg/kg body weight. The assay was carried out in accordance with OECD guideline No. 475. Groups of 6 animal/sex, dose and sampling time received single doses of terephthalic acid dimethyl ester, formulated in 1-percent carboxymethylcellulose, by oral gavage at 0 (control), 500, 1670 or 5000 mg/kg body weight. The volume administered orally was 20 ml/kg body weight, 5000 mg/kg body weight being the maximum administrable dose under the experimental conditions of the study. The positive controls were treated orally with cyclophosphamide at 40 mg/kg body weight. The animals were killed for bone marrow collection 24 hours after administration, 2.5 hours after being treated with colchicine by intraperitoneal injection of 2 mg/kg body weight in order to arrest dividing cells at metaphase. Additional animals treated with terephthalic acid dimethyl ester at 5000 mg/kg body weight were killed at 6 and 48 hours after dosing. For each of 5 animals group, 1000 bone marrow cells were scored for mitotic index determination and 100 metaphases were examined with respect to structural chromosome aberrations. Terephthalic acid dimethyl ester treatment did not give rise to any increase in the incidence of structural chromosome aberrations when compared with the negative control. Analysis of chromosome aberrations was performed both including and excluding gaps. Animals treated with terephthalic acid dimethyl ester at 5000 mg/kg body weight had a slightly lower mitotic index 6 hours after administration than did the negative controls, a finding indicative of mild cytotoxicity on the part of the chemical. As expected, the positive control cyclophosphamide induced chromosome aberrations (CCR, 1990).

Terephthalic acid dimethyl ester induced no sex-linked recessive lethal mutations after feeding or injection in a test on *Drosophila melanogaster*. The injection solution (0.7-percent saline) or food (5-percent sucrose solution) was supplemented with 99% pure terephthalic acid dimethyl ester, dissolved in Tween 80 (polysorbate 80), Pluronic F68 (an ethylene oxide/propylene oxide copolymer) and/or ethanol. Wild-type Canton-S male flies received food containing 0 (control) or 1000 ppm terephthalic acid dimethyl es-

ter for 72 hours and were subsequently each transferred to 3 fresh Basc female flies every 2 to 3 days to obtain a total of three broods. Alternatively, males were injected with 0 (control) or 400 ppm and mated in the same manner, starting 24 hours after injection. The concentrations were selected on the basis of previous toxicity and solubility tests (no further details). Treatment with terephthalic acid dimethyl ester affected neither parental mortality (0 and 3%) nor parental sterility (0%). In the 5630 to 6055 offspring from the F_1 matings, frequencies of sex-linked recessive lethal mutations of 0.02% (feeding, control: 0.04%) and 0.05% (injection, control: 0.07%) were not increased (Foureman et al., 1994).

On the other hand, Goncarova et al. (1984) reported obtaining a positive result with terephthalic acid dimethyl ester (commercial product, purity not specified) in the dominant-lethal test on *Drosophila melanogaster* (wild-type strain Berlin). Males of the wild-type Berlin strain kept on food with 150 or 250 mM terephthalic acid dimethyl ester as adult flies (imagos) or raised on food containing terephthalic acid dimethyl ester at 50, 150, 250, 350 or 500 µM, were each separately mated with 5 virgin females. The males and females were transferred to fresh nutrient medium together after a 24-hour mating period. Another 24 hours later the females alone were transferred to fresh nutrient medium. The numbers of undeveloped eggs and flies dying at the larval or pupal stages were determined. According to the investigators' analysis, there was a two- to three-fold increase in the incidence of dominant lethal mutations. However, no strict concentration dependence was observed with regard to mortality rates at the egg, larval or pupal stages (Goncarova et al., 1984). The details of the conduct of the study remain obscure due to inaccurate documentation. For instance, it is unclear whether the males which fathered the males bred on nutrient media containing terephthalic acid dimethyl ester had themselves also been treated with the chemical, and whether the chemical was contained in all nutrient media on which the females laid their eggs or on which development to the imago stage took place. Moreover, no details were reported as to whether the poor solubility of terephthalic acid dimethyl ester was overcome by pre-dissolving the chemical in a solubiliser, how the controls were treated and what criteria were used to select the test concentrations. The investigators only stated that the concentrations they used on the adult insects were nontoxic in preliminary experiments, but resulted in high egg mortality rates (70 to 80%).

7.7 Carcinogenicity

A 2-year carcinogenicity study in Fischer-344 rats and B6C3F1 mice conducted in the context of the US National Toxicology Programs (NTP) evaluated terephthalic acid dimethyl ester as not carcinogenic under the conditions of the study. Groups of 50 animals per sex, dose and species were given feed containing 2% corn oil and 0 (control), 2500 or 5000 ppm technical-grade terephthalic acid dimethyl ester. The intake of terephthalic acid dimethyl ester based on food consumption and body weights was not calculated. It is estimated, however, that intake of terephthalic acid dimethyl ester was approx. 0 (control), 167 or 333 and approx. 0 (control), 357 or 714 mg/kg body weight/day for rats and mice, respectively. Dose levels were selected on the basis of previously conducted 90-day range-finding studies (see Section 7.5; NCI, 1979), in which administration of feed containing 0 (controls), 1750, 2500, 5000, 10000 or 20000 ppm to groups of 10 animals/sex, dose and species yielded no appreciable findings except for slightly retarded body weight gain in rats treated at 10000 or 20000 ppm, slightly increased mortality (3 out of 20) among 20000 ppm mice and dose-independent diffuse hepatocyte hypertrophy in all dose groups of rats and mice. At treatment initiation, rats and mice in the carcinogenicity study were approx. 7 and approx. 8 weeks old, respectively. Rats and mice were treated with terephthalic acid dimethyl ester for 103 weeks and kept under observation for a period of approx. 2 weeks before being sacrificed for macroscopic and histopathological examination at study weeks 105 and 106 (rats) or 104 and 105 (mice). Throughout the treatment and observation periods, animals were observed and clinical signs, body weights and food consumption recorded at regular intervals. No clinical chemistry or haematology parameters were determined. Administration of terephthalic acid dimethyl ester had no effect on either food consumption, mean body weights or survivals of rats or mice. Clinical observation also yielded no findings which the investigators considered to be related to treatment. The only observations were that, compared with controls, female mice more frequently showed alopecia while male mice exhibited injuries that were attributed to fighting. Furthermore, the US EPA pointed out in a risk assessment of terephthalic acid dimethyl ester (EPA, 2001) that treatment with the chemical resulted in a dose-related increase in the incidence of chronic kidney inflammation in male mice (4 out of 49 and 11 out of 49, control: 2 out of 49). The investigators for the NTP study themselves made no mention of chro-

nic kidney inflammation as a treatment-related finding. There was no significant difference in incidence or type of degenerative, proliferative and/or inflammatory kidney lesions occurring in male and female rats treated with terephthalic acid dimethyl ester as compared with controls. Of the male mice treated with terephthalic acid dimethyl ester, 8 out of 49 in the low dose group and 13 out of 49 in the high dose group showed primary lung tumours (alveolar/bronchiolar adenomas or carcinomas). Compared with the control male mice in the terephthalic acid dimethyl ester study, which had an inordinately low lung tumour incidence of 1 out of 49, the lung tumour incidence was statistically significantly increased in mice treated with the chemical. Other control groups from carcinogenicity studies concurrently conducted in male B6C3F1 mice in the same laboratory exhibited markedly higher lung tumour incidences (5 out of 49, 6 out of 46 and 9 out of 49). When lung tumour incidences noted in the groups treated with terephthalic acid dimethyl ester were compared with the incidences in the latter control groups there were no statistically significant differences. The lung tumour incidences in male rats treated with terephthalic acid dimethyl ester also fell within the range of the historical controls (2 to 34%, see Rall, 1981). In female mice, malignant lymphomas were noted in 5 out of 50 females in the low dose group, 27 out of 49 females in the top dose group and 16 out of 48 controls. The control group for another study concurrently conducted in the same laboratory had 20 out of 49 female mice with malignant lymphoma and leukaemia. Statistical analysis of the incidence of lymphomas in female mice treated at 5000 ppm terephthalic acid dimethyl ester did not indicate an unequivocal increase. The investigators pointed out that the doses administered may not have been sufficiently high to provide maximum test sensitivity. They concluded from their findings that terephthalic acid dimethyl ester was not carcinogenic to rats or mice under the conditions of the study. This evaluation was confirmed by re-analysis of the study data, which included independent histopathological re-examination of the mice's lungs (NCI, 1979; Rall, 1981).

A cell transformation assay was conducted in mouse fibroblasts (BALB/c-3T3 cells, A31-1-13 clone) according to a standard protocol in order to test terephthalic acid dimethyl ester and 167 other chemicals for their potential to induce cell transformation. In order to enhance the solubility of terephthalic acid dimethyl ester and obtain a fine particulate suspension of the undissolved chemical in the culture medium, the latter was warmed to

37 °C for 30 minutes, sonicated and supplemented with Pluronic F68 (an ethylene oxide/propylene oxide copolymer) even though, according to the investigators, the ester is temperature-sensitive and reacts with water. By this procedure it was possible to dissolve terephthalic acid dimethyl ester at 125 µg/ml (approx. 0.64 mM). The investigators discussed the possibility that the structure of the test substance could have been altered by the way it was formulated in the medium. However, they did not perform any analyses to address this question. The study assessed the cytotoxicity of terephthalic acid dimethyl ester by means of the “Standard Clonal Survival Assay” and the “Co-culture Clonal Survival Assay”. Terephthalic acid dimethyl ester was noncytotoxic (LC_{50} > 15,4 mM). The cell-transforming activity was assessed in two independent tests, each comprising 20 cell cultures/concentration, with concentration levels far exceeding solubility. In the first experiment with 0 (negative control), 0.644, 1.29, 2.58 and 5.15 mM, the cell transformation rate was increased at the top two test concentrations, this transformation response being evaluated as “sufficient positive”. However, the result was not reproduced in the second experiment, which used concentrations of 0 (negative control), 1.29, 2.58, 3.87 and 5.15 mM; there was only a concentration-independent increase in cell transformation rate at the lowest concentration (“limited activity”). Overall, the investigators evaluated terephthalic acid dimethyl ester as having indeterminate activity in the cell transformation assay. Benzo(a)pyrene as the positive control showed the expected cell-transforming activity (Matthews et al., 1993).

7.8 Reproductive toxicity

The reproductive toxicity of terephthalic acid dimethyl ester was studied in Long-Evans rats. Groups of 20 male rats from a subchronic feeding study (see Section 7.5; Krasavage et al., 1973) received diet containing terephthalic acid dimethyl ester at concentration levels of 0.25, 0.5 or 1% over a period of 115 days before being mated for one week under continued administration of test substance with groups of 20 virgin females fed corresponding diets for 6 days before mating. Females continued to receive test substance until the end of lactation (day 21 postpartum). Male rats treated with terephthalic acid dimethyl ester showed normal mating behaviour, and 95 to 100% of females with positive proof of copulation became pregnant. Gestation, litter sizes and mortality of pups up to weaning at postpartum day 21

were not affected by treatment with terephthalic acid dimethyl ester. The one treatment-related effect noted was a significant dose-dependent reduction in body weight of the pups at 21 days postpartum in the intermediate and top dose groups. The 0.25% dietary dose of terephthalic acid dimethyl ester yielded no findings in the one-generation study (Krasavage et al., 1973).

A teratogenicity/embryotoxicity study, which was conducted as a limit test in accordance with OECD guideline No. 414, gave no indication of embryotoxicity or teratogenicity for terephthalic acid dimethyl ester. A group of 20 female Wistar rats received terephthalic acid dimethyl ester at 1000 mg/kg body weight once daily by oral gavage on days 7 to 16 of gestation. A control group of another 20 animals received the vehicle only (starch mucilage, 5 ml/kg body weight). Behaviour, general condition, food consumption and maternal body weight gain were checked during the study. The dams were sacrificed on day 21 of gestation, caesarean section was performed and the numbers of corpora lutea, implantations, early and late resorptions, live and dead foetuses were determined and placental weights and diameters of foetal resorptions recorded. Furthermore, the pregnant females were necropsied and their organs macroscopically examined. The scope of foetal examinations encompassed determinations of sex, weight, crown-rump length, signs of life, appearance and externally visible abnormalities and, following appropriate preparation and staining, skeletal and visceral anomalies. The investigations showed that repeated oral administration of terephthalic acid dimethyl ester at 1000 mg/kg body weight during the sensitive phase of organogenesis had no adverse effect on either general maternal health or intrauterine development. The foetuses obtained from the treated group were normally developed and exhibited no externally visible abnormalities or variations or anomalies or variations of the internal organs or skeleton which could have been attributed to treatment with terephthalic acid dimethyl ester. Therefore, the *no effect level* for terephthalic acid dimethyl ester was 1000 mg/kg body weight with regard to maternal toxicity and embryotoxicity/foetotoxicity in the rat (Hoechst, 1986).

In an inhalation study focussing on embryotoxicity/teratogenicity, 30 pregnant albino rats were exposed to a terephthalic acid dimethyl ester concentration of 1 mg/m³ for 24 hours daily throughout pregnancy. The dams, which were examined macroscopically and histopathologically, reportedly exhibited marked toxicity at this concentration level (no further details). The control group consisted of 17 pregnant rats. All dams were killed on day 20

of gestation, numbers of corpora lutea, implantation sites and live and dead foetuses were determined and the foetuses were examined for malformations. There was no indication of embryotoxicity or teratogenicity for terephthalic acid dimethyl ester (Krotov and Chebotar, 1972).

7.9 Effects on the immune system

The sensitising potential of terephthalic acid dimethyl ester (purity not specified) was studied in groups of 7 Wistar rats which were either exposed to terephthalic acid dimethyl ester concentrations of 0 (control), 0.08, 0.4 or 1 mg/m³ (no details of the type of exposure or of analytical verification) 24 hours daily for 3 months or received oral treatment for 30 days with terephthalic acid dimethyl ester at daily dose levels of 0 (control), 0.075, 7.5 or 75 mg/kg body weight. Basophil degranulation, autoimmune haemolytic plaque-forming reaction, complement fixation by antibodies and lymphocyte transformation were studied. The investigators gave no experimental details of the study except that an aqueous solution of terephthalic acid dimethyl ester, a 25-percent aqueous salt extract of lung tissue from inhalation-exposed animals and liver extracts from orally treated animals served as antigens. Absorption of terephthalic acid dimethyl ester via both inhalation and oral exposure reportedly gave dose-dependent positive findings for all tests. As a rule, results did not depend on the duration of treatment. Administration of the γ-globulin fraction of the blood serum from animals exposed in the inhalation study to pregnant rats reportedly resulted in foetal death and increased numbers of foetuses with haemorrhages and rib deformities (no further details). The investigators concluded from their findings that terephthalic acid dimethyl ester had a sensitising effect and that antibodies present in the blood serum caused embryotoxicity (Vinogradov et al., 1986). The study is unsuitable for evaluating the immunotoxic potential of terephthalic acid dimethyl ester because essential details of study conduct and data analysis were not reported.

7.10 Neurotoxicity

No information available.

7.11 Other effects

Uninterrupted exposure of female rats to 0.08, 0.4 or 1 mg/m³ terephthalic acid dimethyl ester for 120 days resulted in reduced activity levels of cAMP metabolic enzymes in the grey matter of the cerebrum. Reductions in enzyme activity were noted for adenylate cyclase at the highest dose level and for phosphodiesterase in all dose groups. Levels of cyclic adenosine phosphate measured in the brain substance from animals exposed to terephthalic acid dimethyl ester were similar to those in the controls (no further details; Davidenko et al., 1982).

An in-vitro oestrogenicity assay in human cells, the E-SCREEN in oestrogen-sensitive MCF-7 breast cancer cells, was negative with terephthalic acid dimethyl ester. As a measure of oestrogenicity, the proliferation of MCF-7 cells was determined in comparison with negative controls and oestrogen-treated positive controls (Sonnenschein and Soto, 1998; Soto et al., 1995).

8 Experience in humans

Neither a single 24-hour dermal application nor 10 applications (of unspecified duration) of an 80-percent oily formulation of terephthalic acid dimethyl ester to the skin of healthy subjects caused pathological reactions (no further details; Massmann, 1966).

In the absence of further details, one source reported that workers producing and processing terephthalic acid dimethyl ester developed pruritic dermatitis and respiratory irritation (American Industrial Hygiene Association, not dated).

An epidemiological study investigated the tumour mortality in workers at a French plant producing polyamide fibres (Nylon), polyethylene terephthalate fibres (Tergal) and polyamide resins since 1952, 1956 and 1982, respectively. The workers had exposure to numerous chemicals (those named being ammonia, adipic acid, hexamethylene diamine, titanium oxide, Raney nickel, manganese and cobalt salts, terephthalic acid and its salts, terephthalic acid dimethyl ester, paraxylene, ethylene glycol and methylene dianiline). The investigators did not specify the levels of exposure. They divided the total study cohort into four subcohorts: Nylon workers, Tergal workers, Maintenance workers and “Unexposed” workers. Of the 3086 workers included in the analysis who were employed at the plant for at least

one year during the period from 1950 to September 1981 (the study closing date for the first analysis), a total of 419 died by July 1986 (the study closing date for the second analysis). For comparison, the death rates for the French male population were obtained from data banks of the World Health Organisation and a French national institute (INSERM, French National Institute of Health and Medical Research). Workers' smoking habits could only be recorded in approximation and smoking habits of the general population were unknown. The investigators assumed that the workers smoked more heavily than the general population. As expected, total mortality for the workers was lower than for the general population (healthy worker effect; SMR 86.1, 95% confidence interval: 78 to 95%). Compared with the general population, mortality for all workers was increased for all cancers (SMR 115.1, 95% confidence interval: 98 to 134%, based on 163 deaths), cancer of the lung (SMR 139.6, 95% confidence interval: 102 to 188%, based on 44 cases) and, marginally significantly, cancer of the urinary bladder (SMR 203.8, 95% confidence interval: 82 to 421%, based on 7 cases). Tumour incidences were not found to depend on the workers' total duration of employment or the time since the start of employment. Those workers who could be assumed to have had the highest exposure to terephthalic acid dimethyl ester (the subcohort of Tergal workers), showed no significant differences in total mortality or mortalities for all cancers, lung cancer or cancer of the urinary bladder when compared with the corresponding mortalities for the general population (Hours et al., 1989).

Examination of 150 workers employed in the production of terephthalic acid dimethyl ester reportedly revealed moderate leukocytosis at the expense of neutrophils in several cases. According to the investigators, the observed changes may also have been caused by other chemical substances in the air (no further details; Kamal'dinova et al., 1962).

9 Classifications and threshold limit values

In the Federal Republic of Germany, the Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area ("MAK-Kommission") of the Deutsche Forschungsgemeinschaft has listed terephthalic acid dimethyl ester in the "Yellow Pages" of the List of MAK and BAT Values 2004 on the suggestion of BG Chemie in order that a MAK value be established for the chemical (DFG, 2004).

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