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Environmental Protection Agency

Evaluation of health hazards by exposure to

Biphenyl

**and proposal of a health-based quality
criterion for ambient air.**

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Title:

Evaluation of health hazards by exposure to Biphenyl and proposal of a health-based quality criterion for ambient air

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Preface

The Danish Environmental Protection Agency has requested an evaluation of health hazards by exposure to Biphenyl, and a proposal of a health based quality criterion for ambient air. This resulted in 2006 in the present report, which was prepared by Lea Tobiassen, Elsa Nielsen and Ole Ladefoged, Department of Toxicology and Risk Assessment, Danish Institute for Food and Veterinary Research, i.e. the present Division of Toxicology and Risk Assessment, National Food Institute, Technical University of Denmark.

The report has been subjected to review and discussion and has been endorsed by a steering committee consisting of representatives from the following Danish authorities:

The Danish Working Environment Authority,
The Danish Ministry of Food, Agriculture and Fisheries (The Faculty of Agricultural Sciences),
The Danish Veterinary and Food Administration,
The National Board of Health, Denmark,
The Danish Environmental Protection Agency

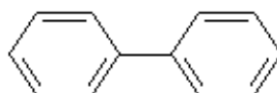
The Danish Environmental Protection Agency
Copenhagen, September 2013.

1 General description

1.1 Identity

Molecular formula: $C_{12}H_{10}$

Structural formula:



Molecular weight: 154.2

CAS-no.: 92-52-4

Synonyms: 1,1'-Biphenyl
Diphenyl
Phenylbenzene
Dibenzene

1.2 Physical / chemical properties

Description: Biphenyl is a colourless to light yellow solid, commonly occurring as flakes, with a strong odour similar to that of geraniums.

Purity: 99.85 % in commercial product

Melting point: 70 °C

Boiling point: 255 °C

Density: 0.992 g/ml (at 20 °C)

Vapour pressure: 0.03 mmHg (4 Pa) at 20 °C

Concentration of saturated vapours: 253 mg/m³ (at 20 °C and 760 mmHg)

Vapour density: -

Conversion factor: 1 ppm = 6.43 mg/m³ (at 20 °C and 760 mmHg)
1 mg/m³ = 0.16 ppm

Flash point: 113 °C

Flammable limits: -

Autoignition temp.: -

Solubility: Insoluble in water

$\log P_{\text{octanol/water}}$: 3.88 - 4.04 (measured)

Henry's constant: $138.6 \text{ Pa} \times \text{m}^3/\text{mole}$ (at $20 \text{ }^\circ\text{C}$)

pK_a -value: -

Stability: -

Incompatibilities: -

Odour threshold, air: $0.0062\text{-}0.3 \text{ mg/m}^3$

Odour threshold, water: 0.00050 mg/l

Taste threshold, water: -

References: Amoores & Hautala (1983), BUA (1990), ChemFinder (2002), CICAD (1999), Ruth (1986).

1.3 Production and use

Biphenyl can be produced through thermal dehydration (at 800°C) of benzene or by distillation from coal tar fuel oil (BUA 1990).

Biphenyl is used as an intermediate in the production of e.g. emulsifiers, optical brighteners, leather tanning agent, plant protection products and plastics, as a heat transfer medium in heating fluids, a dyestuff carrier for textiles and copying paper, as a solvent in pharmaceutical production, and as a fungistatic agent for wood and citrus fruit preservation (CICAD 1999).

1.4 Environmental occurrence

Biphenyl occurs naturally in coal tar, crude oil and natural gas. Production and processing plants of biphenyl containing products, e.g. citrus fruit preservative, creosotes for wood preserving, and waste disposal sites contribute to the environmental occurrence as does exhaust from traffic and heating facilities.

1.4.1 Air

In urban air, concentrations of biphenyl ranged from 1.7 to 26.2 ng/m^3 in Finland in 1985 (BUA 1990), from $12\text{-}119 \text{ ng/m}^3$ (mean 30 ng/m^3) in the US in 1988-89 (Hawthorne et al. – quoted from CICAD 1999), and below 5 ng/m^3 in Greece in 1992 (Karanassios et al. 1994 – quoted from CICAD 1999).

1.4.2 Water

Biphenyl concentrations in the Rhine have declined from 1000 ng/litre in the 1970s to levels below 500 ng/l in 1993-95. Levels in tributary rivers to the Rhine were below 500 ng/l (detection limit) but the Emscher river revealed biphenyl concentrations of 560 ng/l in 1993 and 1600 ng/l in 1994. Some German estuaries had concentrations as low as 1-5 ng/l. (CICAD 1999).

1.4.3 Soil and sediments

Concentrations of biphenyl ranged between 0.1 and 8 mg/kg – depending on the source – in river and estuarine sediments at industrial plants or waste dumps. Soil sampled near a pit for wastewater from oil production in New Mexico, USA contained up to 13 µg/kg. No data on biphenyl concentrations in soil not directly polluted were found. (CICAD 1999).

1.4.4 Foodstuffs

Citrus fruits on the Japanese market treated with biphenyl as a fungistatic agent have been found to contain from 17 to 123 mg biphenyl/kg fruit in the peel and from <0.01 to 0.18 mg biphenyl/kg fruit in the pulp with an average content of 0.06 mg/kg (Isshiki et al. 1982 – quoted from CICAD 1999).

1.5 Environmental fate

1.5.1 Air

Biphenyl is degraded in air by hydroxyl radicals in a photooxidative process with a half-life of about 2 days. Tropospheric ozone and nitrate reactions are expected to be of minor importance, with half-lives calculated to be >80 days and >105 days, respectively. (CICAD 1999).

1.5.2 Water

No data regarding photodegradation of biphenyl in water have been found. Biphenyl is not expected to hydrolyse. (CICAD 1999).

1.5.3 Soil

Laboratory and calculated values for soil sorption coefficient (K_{OC} range from 1100 to 18000 (mean: 4230) indicate low mobility of biphenyl in soil. Thus, the probability of groundwater infiltration is low. Aerobic degradation on soil surface occurs by microbial organisms; and volatilisation is low. (CICAD 1999).

1.5.4 Bioaccumulation

Bioaccumulation of biphenyl of activated sludge has been studied in static tests with yeast, algae, molluscs, daphnia, and freshwater fish, and BCFs ranging between 57 and 540 have been reported. In *Daphnia magna* test, where the BCF at 24 hours was 473, 88% of biphenyl was depurated within additionally 24 hours at

22°C. The potential for bioaccumulation of biphenyl is reduced by evaporation, adsorption to soil/sediment, and degradation, resulting in minor bioaccumulation in aquatic organisms. (CICAD 1999).

1.6 Human exposure

An average daily intake of biphenyl from air has been calculated from measurements in Finnish and Canadian homes to range from 45 to 300 ng/kg b.w. per day (CICAD 1999).

Human exposure to biphenyl through the drinking water ranged in the 1970's between 0.1 and 5 ng/l (BUA 1990). The estimated intake through drinking water is calculated to range from 0.003 to 0.16 ng/kg b.w. per day. (CICAD 1999).

Exposure through the food primarily occurs through intake of biphenyl-conserved citrus fruits, one biphenyl-treated fruit accounting for 113-375 ng/kg b.w. (CICAD 1999). An average intake of 64 ng biphenyl/kg b.w. per day from food was calculated based upon consumption of foodstuffs in Finland (Penttilae & Siivinen 1996 – quoted from CICAD 1999).

Exposure may also occur through contact with consumer products such as creosote-preserved wood, textiles, copying papers, or pharmaceuticals.

2 Toxicokinetics

2.1 Absorption and distribution

No studies on the absorption or distribution of biphenyl were found. However, high recovery percentages in urine (92%) and faeces (7%) of orally administered radio-labelled biphenyl to rats in metabolism studies as well as cases of human poisoning indicate high oral absorption (CICAD 1999).

2.2 Metabolism and elimination

Three male albino rats were dosed orally by gavage with 100 mg/kg ¹⁴C-biphenyl. A total of 92.2% of the radioactivity was recovered after 96 hours. Urinary excretion accounted for 84.8% of the radioactivity (75.8 % within 24 hours) and faecal excretion for 7.3% (5.8% at 24 hours), while only traces were found in expired air. In addition, 0.6% of the dose was found to remain in the tissues. Extraction with sodium bicarbonate indicated that the urinary metabolites were primarily conjugated phenolic metabolites (28.6 % of the dose) and acidic metabolites (25.5%). (Meyer et al. 1976a).

Male albino rats were given 100 mg biphenyl/kg b.w. by stomach tube as a solution in soy oil. Urine and faeces were collected for 4 days and 24 hours, respectively. The total amount of phenolic metabolites found in urine over 96 hours was 29.5%, and the major urine metabolites identified by mass spectrometry and quantified by gas chromatography were 4-hydroxybiphenyl (7.7%) and 4,4'-dihydroxybiphenyl (11.4%). Also 3,4,4'-trihydroxybiphenyl (3.2%) and 3,4'-dihydroxybiphenyl (2.6%) were found in urine. At 24 hours, 5.2% of the dose was found in bile as conjugates of hydroxylation products, mainly of 4-hydroxybiphenyl, 4,4'-dihydroxybiphenyl and 3,4,4'-trihydroxybiphenyl. The same phenolic metabolites were found in faeces, accounting for 4.7% of the dose, with 4,4'-dihydroxybiphenyl as the major metabolite (1.8 %) and lesser amounts of 3,4,4'-trihydroxybiphenyl (1.1%) and 4-hydroxybiphenyl (1.0%). (Meyer & Scheline 1976).

Three male White Land rabbits were dosed 100 mg biphenyl/kg b.w. by gavage, in a solution in soy oil. Urinary recovery attained 49.1% of the dose at 96 hours, with 25.4 % being excreted during the first 24 hours. The urinary excretion consisted of phenolic metabolites, mainly 4-hydroxybiphenyl (35.6%), 3,4-dihydroxybiphenyl accounting for 5.2% and 4,4' dihydroxybiphenyl for 1% of the dose. Conjugation was important as less than 1% 4-hydroxybiphenyl was excreted as the free form. Faecal excretion accounted for 1.6 %, 1.4 % as biphenyl itself. The bile of one rabbit was collected 7 hours after intraperitoneal injection of 100 mg biphenyl/kg b.w. and revealed only one metabolite, 4-hydroxyphenyl, which accounted for 0.3% of the dose given. (Meyer 1977).

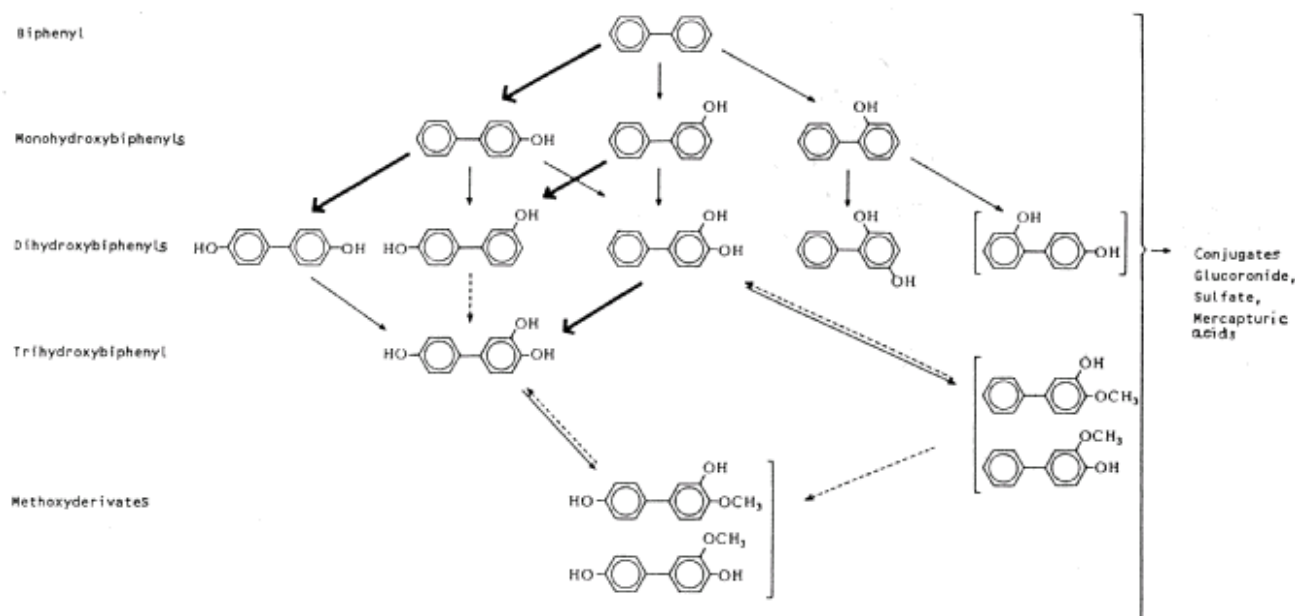
Three male Sff:PIR guinea pigs were given 100 mg biphenyl/kg b.w. by stomach tube, as a solution in soy oil. The phenolic metabolites of biphenyl were quantified, revealing 4-hydroxybiphenyl to be the major urinary metabolite (25.5% at 96 hours), with 3,4-dihydroxybiphenyl and 3-hydroxybiphenyl accounting for 3.2 and 2.7%, respectively. The vast majority of urinary metabolites were excreted during

the first 24 hours, as conjugated hydroxylated biphenyls (23.4% out of 24.8% 4-hydroxybiphenyl at 24 hours), leaving only minor or trace amounts as free hydroxy-compounds. Faecal excretion of unchanged biphenyl represented 14.3% of the dose, adding up to 20.3 % with the phenolic metabolites . Bile was collected 7 hours after dosing two guinea pigs. The three most important urinary phenolic metabolites were also found in bile, which accounted for 3.3% of the dose. (Meyer 1977).

The phenolic metabolites of biphenyl were qualitatively and quantitatively analysed in a study where 2 female and 2 male pigs were dosed 100 mg biphenyl/kg b.w. in soy oil or propylene glycol. The total urinary excretion of phenols 4 days after treatment with biphenyl in soy oil was 27.6% of the dose in females and 44.8% in males. The major urinary metabolite was 4-hydroxybiphenyl (19% in females, 32% in males), 2-hydroxybiphenyl (females 2.7% and males 4.3%), 4,4'-dihydroxybiphenyl (2 and 2.8%, respectively). No effect on the metabolism of biphenyl was seen from treatment with propylene glycol, which has a suppressive effect on the intestinal microflora. No phenolic metabolites of biphenyl were detected in faeces. Percentages of 18.4 and 5.0 of the parent compound were identified in faeces for the female pigs while no biphenyl was detected in faeces from the male pigs. No phenolic metabolites of biphenyl were detected in bile. (Meyer et al. 1976b).

In vitro incubation of biphenyl in liver microsomes from rats, mice, hamsters, guinea pigs, rabbits, dogs, cats and monkeys permitted to isolate 4-hydroxybiphenyl as the main metabolite (BUA 1990).

Figure 1: Proposed metabolism of biphenyl. Modified from BUA (1990).



Thick arrow: *major pathway*
 Thin arrow: *minor pathway*,
 Broken arrow: *theoretical pathway (not verified)*

2.3 Mode of action

No information was found.

3 Human toxicity

3.1 Single dose toxicity

No information was found on systemic effects in humans after single exposure.

3.2 Irritation

Irritation of the eyes, nose and throat has been reported from acute inhalation of 3 or 4 ppm (corresponding to 19.3-25.7 mg/m³) of a mixture of 26.5% biphenyl and 73.5% biphenyl ether (details on exposure duration not specified) (Gerarde 1960 – quoted from IUCLID 2000).

The inhalation irritation threshold was reported to be 7.5 mg/m³ (Ruth 1986). The reference is a table, which does not give any details on the exposure duration or whether the exposure was to vapours or to aerosols.

A single application of 0.5 ml of a 4% biphenyl solution to the skin of the lower arm of two volunteers did not cause irritation; no further details were reported (Macintosh 1945 – quoted from CICAD 1999 and IUCLID 2000).

Application to the forearm of a volunteer of a 23% biphenyl solution in oil 3 times/week for 8 weeks did not result in irritation (Selle 1952 – quoted from CICAD 1999 and IUCLID 2000).

3.3 Sensitisation

In a handbook on occupational diseases, biphenyl is referred as being a skin sensitizer through repeated skin contact. The background for this statement is unknown. (Key et al. 1977 – quoted from IUCLID).

3.4 Repeated dose toxicity

3.4.1 Inhalation

Workers exposed to biphenyl while impregnating citrus fruit wrapping paper complained of nausea, vomiting and coughing. The respiratory tract irritation was proven clinically (bronchial discharge). Exposure levels were not measured. The symptoms were reversible when exposure ceased. (Weil et al. 1965).

One worker died in 1969 after working for 11 years in a plant producing biphenyl-impregnated fruit wrapping paper. The worker had been working with dispensing biphenyl into a mixing container with heated pure paraffin oil. He had also been in charge of cleaning the equipment with trichloroethylene or tetrachloroethylene for 1 hour, 5-10 times yearly. The worker had been exposed to biphenyl both by inhalation and dermally. The cause of death was established to be liver atrophy. A study of the exposure levels at the mill and clinical examination of all 33 exposed workers was then carried out. Levels of biphenyl reached 64.0 mg/m³ behind

the impregnating roller, 74.5 mg/m³ when adding biphenyl into the mixer and 123 mg/m³ when checking a measuring container, while levels in the rest of the mill ranged from 0.6 to 15.5 mg/m³. Trichloroethylene was substituted for tetrachloroethylene in 1968. No measurements of trichloroethylene were available. For tetrachloroethylene, average concentration in 1970 ranged from 9-75 ppm during cleaning procedures. The authors evaluated tetrachloroethylene exposure to be insignificant.

Clinical findings included complaints of headache, fatigue, gastrointestinal symptoms (diffuse pain, nausea, indigestion) and neurological symptoms as numbness and aching of the limbs. Nineteen out of 22 men examined neurologically (e.g., electroencephalogram, cytology of the cerebrospinal fluid, psychological tests, electroneuromyography) showed impaired function of the central and/or the peripheral nervous system (e.g., nerve conductivity). Ten subjects had elevated liver transaminase values. Liver biopsy was taken from 8 men. Five of them showed chronic liver damage with cirrhosis, fibrosis and/or centrilobular fatty changes. The authors concluded that long-term exposure to high concentrations of biphenyl causes central as well as peripheral nervous system and liver damage. (Häkkinen et al. 1973).

A handbook reports that 30 years of occupational exposure to Dowtherm A (a mixture of 26.5% biphenyl and 73.5% biphenyl ether) did not cause any signs of chronic intoxication (Gerarde 1960 – quoted from IUCLID 2000).

3.4.2 Oral intake

A case of chronic hepatitis after oral and dermal exposure is described in section 3.4.3.

3.4.3 Dermal contact

A woman who had worked for 25 years in a citrus packing plant, wrapping fruit with biphenyl-impregnated paper was diagnosed to have chronic persistent hepatitis. A liver biopsy revealed polymorphic inflammatory infiltrate with some eosinophils in the portal and lobular regions. The woman had been exposed to biphenyl both through the skin and orally. No confounding exposure or other causes of liver disease were identified. (Carella & Marini Bettolo 1994).

The case study by Häkkinen et al. (1973) described in section 3.4.1 relates to both inhalation and dermal exposure.

3.5 Toxicity to reproduction

No data were found.

3.6 Mutagenic and genotoxic effects

No data were found.

3.7 Carcinogenic effects

No evidence of a carcinogenic effect of biphenyl was observed in a case study reported by Häkkinen et al. (1973) and described in section 3.4.1.

4 Animal toxicity

4.1 Single dose toxicity

4.1.1 Inhalation

Eight male and eight female rats/group were exposed to 0, 960 or 3740 mg/m³ biphenyl for one hour. Two rats were sacrificed per time point at 1, 3 and 24 hours, and 2, 7 and 14 days after treatment. No mortality occurred during the study. Slight erythema of the ears and paws were seen in both treated groups. Acute oedema and necrosis in the trachea were observed in the high dose group. Both treated groups showed lung oedema and bronchopneumonia; however, these findings were also reported in the controls. (Haley et al. 1959).

No effects were reported in Sprague-Dawley rats exposed to 0.8 or 3 ppm (corresponding to 5.1 or 19.2 mg/m³) biphenyl for 6 hours (Monsanto Co. 1959 – quoted from CICAD 1999).

Twenty mice were exposed to above 43 ppm (corresponding to 275 mg/m³) biphenyl for 4 hours. One animal died, but the death was not considered compound-related. Hyperactivity and mild respiratory discomfort were observed during exposure, but these effects were reversible before the end of the observation period. Slight lung congestion was seen at autopsy. (Sun Co. Inc 1977a – quoted from CICAD 1999 and IUCLID 2000).

4.1.2 Oral intake

Rat oral LD₅₀-values are reported to range from 2400 to 5040 mg/kg b.w. (BUA 1990 and IUCLID 2000). One of the experiment included 60 rats and the calculated LD₅₀ was 3.28 g/kg b.w. Deaths occurred 18 hours to 2 days after treatment. Clinical symptoms included increased respiration rate, lachrymation, loss of appetite, weight loss, and coma. Pathological examination revealed albuminous and fatty hepatocellular degeneration, degeneration of the myocardium, lung congestion, alveolar oedema and interstitial and lobular pneumonitis and severe glomerulotubular nephritis. (Deichmann et al. 1947).

In rabbits, the LD₅₀-value is reported to be 2400 or 2410 mg/kg b.w. (BUA 1990, IUCLID 2000). The same clinical and pathological effects were reported as those in rats mentioned above by the same authors (Deichmann et al. 1947).

4.1.3 Dermal contact

An LD₅₀-value of 2500 mg/kg b.w. in rabbits was reported (IUCLID 2000).

4.2 Irritation

Solid biphenyl was reported not to be irritating to rabbit skin following application to the intact or abraded skin of 6 rabbits (Draize-method). All animals scored 0 for

erythema and oedema (maximum score of 8) both at 24 and 72 hours after application. The authors discuss that the results may be due to the poor penetrating power of biphenyl in solid form. (Haley et al. 1959)

Following the Draize-method, 0.1 ml of a mixture of terphenyls and biphenyl containing 17% biphenyl was applied to one eye of two rabbits and corn oil to the other eye. No effects were seen in the conjunctiva, the cornea, or the iris. (Haley et al. 1959).

In another eye irritation test in one rabbit, 10 mg biphenyl was instilled into the eye. Slight conjunctival irritation occurred after 24 hours. (Monsanto 1967 – quoted from IUCLID 2000).

4.3 Sensitisation

Three albino Guinea pigs were exposed intra-dermally to 0.05 ml biphenyl in corn oil 3 times per week for three weeks. Two weeks later, intradermal injection of 0.05 ml 16% biphenyl in corn oil produced inflammation, necrosis and scar formation at the injection sites. The inflammatory reaction extended into the surrounding dermis, subcutaneous fat and skeletal muscle layer and included oedema and infiltration with polymorphonuclear cells focally rich in eosinophiles, with a few lymphocytes and histiocytes. The eosinophilic infiltration may be an indication of an allergic response. However no conclusion on the sensitising potential of biphenyl could be made because of the severe inflammatory response following intradermal injections. (Haley et al. 1959).

4.4 Repeated dose toxicity

4.4.1 Inhalation

Four, 6 and 10 Sprague-Dawley rats were exposed 7 hours per day for 62, 46 and 64 days, respectively, to averages of 5, 40 and 300 mg biphenyl /m³ as a 50% biphenyl/celite dust (a diatomaceous earth product). No signs of toxicity were seen in the low exposure group. The animals of the two highest dose group showed irritation of the mucous membranes with serosanguineous discharge from the nose. One out of 6 animals at the mid-dose and 5 out of 10 animals in the high dose group died; the autopsy showed severe inflammatory bronchopulmonary changes including emphysema, congestion, oedema, bronchitis, lobular and interstitial pneumonia and multiple abscesses of the lungs. Minor changes in the liver and kidneys – no details given – were also reported. (Deichmann et al. 1947).

Male and female mice exposed to 25 or 55 ppm (160 or 350 mg/m³) biphenyl for 7 hours/day, 5 days/week for 2 weeks showed no histopathological changes in the lung, trachea, liver, kidney or spleen. (Sun Co. Inc. 1977b – quoted from CICAD 1999).

Groups of 50 male and female CD-1 mice exposed to concentrations of 0, 25 or 50 ppm biphenyl (corresponding to 0, 160 or 320 mg/m³) for 7 hours/day, 5 days/week for 13 weeks showed hyperaemia and focal haemorrhage in the lung and increased hyperplasia of the tracheal epithelium. The effects were also present in the controls and were attributed to the use of hot air in the aerosol preparation. (Sun Co. Inc. 1977c – quoted from CICAD).

Twelve mice were exposed 7 hours/day, 5 days/week over 92 days (62 exposures) to biphenyl dust on celite, at a concentration of 5 mg biphenyl/m³. All mice showed signs of irritation of the upper respiratory tract. Two mice died, revealing inflammatory bronchopulmonary changes as described above, in rats, by the same authors. (Deichmann et al. 1947).

Groups of 3 albino rabbits were exposed to dust containing 50% biphenyl on celite at concentrations of 40 or 300 mg biphenyl/m³, 7 hours/day over 68 days (46 exposures) or 94 days (64 exposures), respectively. No effects were seen. (Deichmann et al. 1947).

4.4.2 Oral intake

Several studies on biphenyl following repeated oral dosing are available. These data are described below and summarised in Table 1.

4.4.2.1 Rats

Groups of SPF-Wistar rats were fed 0, 50, 150, 300 or 450 mg biphenyl/kg b.w. semi-synthetic diet or 0, 50, 150, 300, 500 or 1000 mg/kg b.w. commercial chow for 21 days. The relative kidney weights were significantly increased in all groups treated with the semi-synthetic diet and at the two highest dose groups fed the commercial chow. These two groups were sacrificed after 14 days due to heavy weight loss. Urine volume and specific gravity was measured in both control groups, in the 150 mg/kg semi-synthetic and in the 500 and 1000 mg/kg commercial diet fed groups. The two parameters were found to be elevated in all the treated groups analysed. Renal cysts were recorded from 150 in the semi-synthetic treated groups and in the high dose group of the commercial chow treated animals. The authors therefore set NOELs for kidney effects at less than 50 mg/kg b.w. for the semi-synthetic diets fed animals and 300 mg/kg b.w. for the commercial chow fed rats. (Søndergaard & Blom 1979).

Rats were exposed through the diet to 0, 0.1, 0.5 or 1% biphenyl (corresponding to approximately 0, 75, 375 or 750 mg/kg b.w./day) for 26 days. No effects were seen at the low dose. In the two highest dose groups, the following effects were reported: progressive polyuria, increases in urine turbidity and in urinary precipitate, occurrence of 4-hydroxybiphenyl and its glucuronide in the precipitate and positive benzidine test, indicative of blood traces in the urine. The findings were largely reversible within the 28 days post-treatment period. (Booth 1956 – quoted from Booth 1961 and IUCLID 2000).

Groups of 10 Male Fischer 344 rats were exposed through the diet to 0 or 0.5% biphenyl (corresponding to 0 or ca. 252 mg/kg b.w./day) for 4 or 8 weeks. No clinical changes were reported, but body weights were significantly decreased in the treated animals. The number of microcalculi (consisting of *p*-phenylphenol) in urine sediment was strongly increased at 4 weeks and histopathology at 8 weeks revealed simple hyperplasia of the bladder epithelium with 4-8 layers of transitional cells. Scanning electron microscopy performed at 8 weeks revealed rounded cells with rosy or leafy microridges on the luminal surface of the bladders. The microvilli were uniformly shortened in 5 out of 5 animals. At 4 weeks, DNA synthesis was significantly elevated in the bladder. The authors consider the promoting effect on the bladder epithelium to be related to mechanical stimulation by the microcalculi. (Shibata et al. 1989a).

Male and female Wistar rats were administered diet containing 0, 0.125, 0.25, 0.5, 1 or 2 % biphenyl (estimated intakes of 0, 94, 188, 375, 750 or 1500 mg/kg b.w./day) for 10 weeks. Dose dependent effects included reduction in weight gain, increased serum activities of liver enzymes and increase in blood urea nitrogen (BUN). (Takita 1983 – quoted from CICAD 1999).

Rats receiving 0.01%, 0.03% or 0.1% (according to IUCLID corresponding ca. 7.5, 22.5 or 75 mg/kg b.w./day) biphenyl in the diet for 3 months showed no significant differences from controls with respect to growth rate, organ weights, BUN or microscopy of various organs. No details were given in the reference (Undated report from Stanford Research Institute – quoted from Ambrose et al. 1960).

Forty rats/sex per group were exposed through the diet to 0, 0.1, 0.25 or 0.5% biphenyl (according to CICAD 1999 corresponding to 0, 75, 188 or 375 mg/kg b.w./day) for 165 days, with interim sacrifice of 5 animals/sex/dose group at day 30, 60 and 120. At day 165, ten animals/sex fed 0.5% biphenyl were returned to control diet for 30 or 60 days. At the top dose, increase in volumes of urine and precipitate was significant from day 27 and throughout the treatment period. The findings were less pronounced at the lower doses. Urine and precipitate volumes had decreased markedly in the recovery period and were practically normal 30 days after exposure. Histopathology of kidneys of the two lowest doses groups showed no changes as compared to controls. At 30 days, one high-dose male had small cysts and dilated tubules, and two females mild tubular dilation. The effects progressed to include all female and three of five males at 60 days, and all animals of the high dose sacrificed at 120 days. Animals of the recovery groups showed less marked tubular dilations and a few scar, indicating reversibility of the effect. (Booth et al. 1961).

Twenty rats/group were fed diet containing 0 or 0.5% biphenyl (according to CICAD 1999 corresponding to 0, 375 mg/kg b.w./day) for 4, 8, 16 or 24 weeks. Reduction in mean body weights was observed in the treated animals from week 1. Absolute and relative kidney weights were significantly higher at each time-point in the treated group. Measurement of DNA synthesis in renal papilla and pelvis after 4 weeks of treatment did not reveal any elevation. Histopathology revealed focal calcification of the renal medulla, but no lesions of the renal papilla and pelvis. In the urinary bladder, simple hyperplasia was seen in 5 out of 5 biphenyl treated rats investigated at weeks 16 and 24, and papillary or nodular hyperplasia in 3/5 rats at week 16 and 5/5 animals at week 24. Urinalysis revealed microcalculi formation in the treated animals. (Shibata et al. 1989b).

Rats were exposed 36 weeks to 0 or 0.5% (corresponding to 0 or 375 mg/kg b.w.) biphenyl in the diet. Body weight gain reduction was reported in the treated group. Urine pH and sodium content of urine increased after 4 and 8 weeks of treatment, respectively. The urinary sediment was found to consist mainly of 4-hydroxybiphenyl. There was stone formation in the urinary bladder, but no histopathological findings in the bladder, liver or kidneys. (Kurata et al. 1986 – quoted from IUCLID).

Exposure of rats to 0.5% biphenyl in the diet (corresponding to 375 mg/kg b.w./day) for 36 weeks caused increase in relative kidney weights and in the incidence of calculi in the urethra, the bladder and the kidneys. No effects were seen at 0.13% (corresponding to 94 mg/kg b.w./day). (Shiraiwa et al. 1989 – quoted from CICAD 1999).

Fifty male and 50 female Wistar rats/group were fed 0, 0.25% or 0.5% biphenyl in the diet (corresponding to 0, 188 or 375 mg/kg b.w./day) for 75 weeks. Weight

gain was reduced in a dose-dependent way, as were alterations in serum activities of aspartate and alanine transaminase and of lactate dehydrogenase and of blood urea nitrogen. The low dose group showed haematuria from week 16, and there was a dose-dependent increase in number of calculi in the ureters and in the kidneys. At the top dose, the incidence of calculi in the bladder was also increased, with simple or diffuse hyperplasia and papillomatose of the bladder epithelium. Relative kidney weights of the females of the top dose were increased. Kidneys with stones revealed obstructive pyelonephritis, tubular atrophy and fibrosis. (Takita 1983, Shiraiwa et al. 1989 – both quoted from CICAD 1999).

In a two year feeding study using 50 Wistar rats/sex/group with doses of 0, 0.063 and 0.125% (corresponding to 0, 47 or 94 mg/kg b.w./day), there was a dose-dependent reduction in weight gain and alterations in serum activities of aspartate and alanine transaminase and of lactate dehydrogenase. No urotheliasis was reported. (Takita 1983 – quoted from CICAD 1999).

Fifteen albino rats/sex/group were exposed through the diet to 0, 0.001, 0.005, 0.01, 0.05, 0.1, 0.5, or 1% biphenyl (according to IUCLID 2000 corresponding to ca. 0, 0.8, 3.8, 7.5, 38, 75, 375 or 750 mg/kg b.w./day) for 2 years. In the two highest dose groups, mortality was clearly increased from about 1 year of exposure. Also, food consumption was decreased, growth was impaired and haemoglobin values lowered in these dose groups. Mean liver and kidney weight were increased at the top dose in females and at the two highest doses in males. Histopathological examination of these two dose groups revealed important changes in the kidney of males and females including scarification, lymphocyte infiltration and atrophy or pronounced dilation of the renal tubules containing polymorphonuclear leucocytes. Calculi were frequent in the dilated renal pelvis. Hydronephrosis was common especially in males, together with squamous metaplasia of the epithelium. In groups dosed 0.1% or less, slight effects on survival, food consumption and body weights were seen. Histopathology of animals of these groups revealed only occasional small scars in the kidneys and focally dilated renal tubules in both sexes, while there was a higher occurrence of hydronephrosis and deposits in the renal pelvis in the males. However, the incidence of these effects was not different from the controls. (Ambrose et al. 1960).

A 2-year chronic/carcinogenicity study was performed according to standard protocols with F344/DuCrj-rats, using diets containing 0, 0.05, 0.15 or 0.45% biphenyl (corresponding to 0, 38, 113 or 338 mg/kg b.w./day). Levels of serum enzymes and blood urea nitrogen were increased in relation to the dose. Haemoglobin concentration and haematocrit were decreased in the two highest dose groups. No information on the amplitude of the effects or their statistical significance were given in CICAD, however, a LOEL for blood effects 38 mg/kg b.w./day was derived. The incidence of hyperplasia of the urinary bladder epithelium was elevated in both sexes of the high dose group, the effect being more pronounced in males than in females. Calculi in the bladder were present in 43 out of 50 high dose males and 8/50 females. No other treated or control group had calculi. A dose-response related hyperplasia of the renal pelvis and mineralisation of the renal papillae and pelvis were seen in male and females from 113 mg/kg b.w./day. The occurrence of stones in the kidney was substantially increased in males of the high dose group (13/50), while high dosed females had a moderate increase (3/50) and no stones occurred in any other treated groups or controls. (Japan Bioassay Research Centre 1996 – quoted from CICAD 1999).

4.4.2.2 Mice

Male B6C3F₁-mice showed no changes in urinary pH or in levels of DNA synthesis in the urinary bladder after administration of 0 or 10% (corresponding to 0 or 1500 mg/kg b.w./day) over 8 weeks. The concentration of sodium in urine was significantly lower than controls only at week 4. (Tamano et al. 1993 – quoted from CICAD 1999).

In a chronic/carcinogenicity study, Crj:BDF₁-mice were given diets containing 0, 0.07, 0.2 or 0.6 % biphenyl/kg (equivalent to 0, 100, 300 or 900 mg/kg b.w./day) for 104 weeks. Body weight gain and food consumption were reduced in the high-dose animals. In the low-dose group, there were degenerative changes of the respiratory epithelium of the nasal cavity (LOEL 100 mg/kg b.w./day). The mid-dose mice showed degeneration of the epithelium of the nasopharynx (LOEL 300 mg/kg b.w./day). Dose-dependent changes in serum enzyme and urea nitrogen levels were reported from the low dose. Females of the two highest dose groups had increased incidence of basophilic cell foci in the liver. The effect was not dose dependent. Degenerative changes in the kidney were reported in the mid-dose females and the high-dose males and included increased mineralisation of the inner stripe of the outer medulla and increase in desquamation of the epithelium of the renal pelvis. Carcinogenicity is described in section 4.5.2. (Japan Bioassay Research Centre 1996 – quoted from CICAD 1999).

4.4.2.3 Rabbits

Five rabbits were dosed with 1000 mg biphenyl/kg b.w. by gavage 2-3 times per week until death occurred, after 4 to 21 doses. No significant changes were recorded in the number of erythrocytes, number and types of leucocytes or the haemoglobin content of the blood. (Deichmann et al. 1947).

4.4.2.4 Dogs

Dogs were administered 0, 2.5 or 25 mg biphenyl per kg b.w./day 5d/w for 52 weeks. No adverse effects were reported in the treated groups on appearance, food intake or at macroscopic or microscopic examination. No details are reported. (Hazleton et al. – quoted from IUCLID 2000)

4.4.2.5 Monkeys

Monkeys treated with 0, 0.01, 0.1 or 1% biphenyl in the diet for one year showed increased liver weights at the high dose as the only significant effect of treatment. (Unpublished report from Stanford Research Institute – quoted from Ambrose et al. 1960).

4.4.3 Dermal contact

Rabbits were exposed to biphenyl on intact or abraded skin 8 hours/day, 5 days/week over 6 weeks (30 times). No irritation, sensitisation or histopathological changes in internal organs or skin were reported. (Report from Stanford Research Institute 1953 – quoted from Ambrose 1960 and CICAD 1999).

A 25% preparation of biphenyl in olive oil was applied to a shaved area of approximately 150 cm² of the abdomen of albino rabbits 2 hours/day, 5 days/week for 4 weeks (twenty times), at a dose of 500 mg biphenyl/kg b.w. One out of 7 rabbits

Table 1: Effects observed in experimental animals following repeated oral exposure

| Species/ strain (number) | Doses (mg/kg b.w./day) | Duration (weeks) | Kidney (mg/kg b.w./day) | Urine / bladder (mg/kg b.w./day) | Other effects (mg/kg b.w./day) | Reference |
|--------------------------|--|------------------|--|---|--|---------------------------------------|
| Rats/ Wistar | 0, 50, 150, 300, 450 – diet a or b | 3 | Renal cysts a: LOAEL 150 b: LOAEL 450 | Urine volume and gravity elevated all groups a: LOAEL 50 b: LOAEL 300 | Weight loss a: NOAEL 450 b: NOAEL 150 | Søndergaard & Blom (1979) |
| Rats | 0, 75, 375, 750 | 4 | | Polyuria, increased turbidity and precipitate (4-hydroxybiphenyl), blood traces in urine LOEL 375 | | Booth (1956) |
| Rats/ Fischer (10/group) | 0, 252 | 4 or 8 | Not examined | Microcalculi (<i>p</i> -phenylphenol), simple hyperplastic urothelium with increased DNA-synthesis, short microvilli | Body weight decrease | Shibata et al. (1989a) |
| Rats/ Wistar | 0, 94, 188, 375, 750, 1500 | 10 | | | Body weight gain depression, liver enzyme and BUN increase LOAEL 94 | Takita (1983) |
| Rats | 7.5, 22.5, 75 | 14 | No effects on weights or microscopy NOEL 75 | No effects on weights or microscopy NOEL 75 | Body weight gain normal, BUN normal NOEL 75 | Stanford Research Institute (Undated) |
| Rats (40/sex/group) | 0, 75, 188, 375 | 4, 8, 17 or 24 | ♂: cysts and dilated tubules ♀: dilated tubules LOEL 375 | Urine volume and turbidity increase, precipitates, sediment with 4-hydroxybiphenyl LOEL 375 | | Booth et al. (1961) |
| Rats (20/group) | 0, 375 | 4, 8, 16 or 24 | Absolute and relative weight increase, no increase in DNA synthesis at week 4, focal medullar calcification LOAEL 375 | Urothelium simple hyperplasia at week 16, progressive papillary/ nodular hyperplasia, microcalculi LOAEL 375 | Body weight depression LOAEL 375 | Shibata et al. (1989b) |
| Rats | 0, 375 | 36 | No histopathological lesions | Urine pH decrease and Na ⁺ increase, urinary sediment (4-hydroxy-biphenyl) and stone formation, no histopathological lesions | Body weight gain depression No histopathological lesions | Kurata et al. (1986) |

| Species/ strain (number) | Doses (mg/kg b.w./day) | Duration (weeks) | Kidney (mg/kg b.w./day) | Urine / bladder (mg/kg b.w./day) | Other effects (mg/kg b.w./day) | Reference |
|-----------------------------|------------------------------------|------------------|--|---|---|---------------------------------------|
| | | | | LOAEL 375 | | |
| Rats | 94, 375 | 36 | Increased relative weights, calculi in kidney and urethra LOAEL 375 | Calculi | | Shiraiwa et al. (1989) |
| Rats/ Wistar (50/sex/group) | 0, 188, 375 | 75 | ♀: increased weights ♀ and ♂: dose-dependent occurrence of urethra and kidney calculi, obstructive pyelonephritis, tubular atrophy and fibrosis LOEL 188 | Haematuria LOEL 188 Calculi, epithelium hyperplasia and papillomas LOEL 375 | Dose-dependent weight gain depression and liver enzyme increase | Takita (1983), Shiraiwa (1989) |
| Rats/ Wistar (50/sex/group) | 0, 47, 94 | 104 | Not reported | No urotheliasis | Reduced weight gain, altered liver enzymes levels | Takita (1983) |
| Rats (15/sex/group) | 0, 0.8, 3.8, 7.5, 38, 75, 375, 750 | 104 | Increased weights, scarification, lymphocyte infiltration, tubular dilation/atrophy, hydro-nephrosis, epithelium metaplasia. No tumours LOAEL: 375 | No dose-response | Increased mortality, food intake, body weights and body weight gain depression, haemoglobin depression, lung tumours LOAEL 375 | Ambrose et al. (1960) |
| Rats | 0, 38, 113, 338 | 104 | Hyperplasia and mineralisation of pelvis epithelium and papillae LOAEL 113 Stones (mostly ♂♂) LOAEL 338 | Hyperplasia of urothelium and urethra epithelium, calculi (mostly ♂♂) LOAEL 338 Papillomas/ carcinomas in ♂♂ at 338 | Liver enzymes and BUN increase dose-related, haemoglobin and haematocrit decrease dose-related LOAEL blood: 38 | Japan Bioassay Research Centre (1996) |
| Mice | 0, 100, 300, 900 | 104 | Desquamation and mineralisation No tumours LOAEL: 300 | No tumours | Food consumption/ body weight gain depression LOAEL 900 Nasal epithelium degeneration LOAEL 100 Basophilic cells in liver of ♀♀ | Japan Bioassay Research Centre (1996) |

| Species/ strain (number) | Doses (mg/kg b.w./day) | Duration (weeks) | Kidney (mg/kg b.w./day) | Urine / bladder (mg/kg b.w./day) | Other effects (mg/kg b.w./day) | Reference |
|--------------------------|----------------------------|------------------|-------------------------|----------------------------------|---|-----------------------------|
| | | | | | LOAEL 100 Liver tumours | |
| Dogs | 0, 2.5, 25 | 52 | | | No effects on food intake, macroscopy or microscopy | Hazleton et al. |
| Monkeys | 0, 0.01, 0.1 or 1% of diet | 52 | | | Increased liver weights | Stanford Research Institute |

died after 8 applications. Body weight gains were reduced. No skin effects were seen. Minimal Histopathological changes in the heart, liver, kidneys and some cases of splenic changes were recorded including loss of pulp cells, with neutrophilic polymorphonuclear leucocytic infiltration, hypoplasia and occasional hyaline necrosis of the follicles and increased activity of the reticuloendothelial cells. No controls were used. (Deichmann 1947 – quoted from CICAD 1999 and IUCLID 2000).

4.5 Toxicity to reproduction

4.5.1 Inhalation

No data were found.

4.5.2 Oral intake

4.5.2.1 Fertility

Ten female and 5 male weanling rats were given diet containing 0 or 0.1% biphenyl (estimated in CICAD 1999 to correspond to 0 or 75 mg/kg b.w./day) and 9 female and 3 male weanling rats 0.5% biphenyl containing diet (estimated in CICAD to correspond to 375 mg/kg b.w./day) from 60 days before mating until weaning of the offspring. Another experiment used 90 day-old rats, dosing 8 females and 4 males with 0 or 0.1% biphenyl and 9 females and 3 males with 0.5% biphenyl through the diet from 11 days before mating until weaning of the offspring. No significant differences were seen in either experiment in the number of pregnant dams or in litter sizes in the treated groups when compared to control groups. (Ambrose et al. 1960).

In an unpublished three generation study in rats fed dietary levels of 0.01, 0.1 or 1% (corresponding to ca. 7.5, 75 or 750 mg/kg b.w./day), fertility, litter size and growth rate decreases were reported in the high dose group, while no effects were seen in the lower dose groups. No details were available. (Undated study by Stanford Research Institute – quoted from CICAD 1999).

No histopathological changes were observed in the reproductive systems of rats or mice administered biphenyl at 500-4500 mg/kg diet (approximately corresponding to 50-450 mg/kg b.w./day for rats and 75-675 mg/kg b.w./day for mice) for 2 years (Japan Bioassay Research Centre 1996 – quoted from CICAD 1999).

4.5.2.2 Developmental toxicity

Groups of 18-29 female Wistar rats were treated by gavage with 0, 125, 250, 500 or 1000 mg biphenyl/kg b.w. in corn oil on days 6 through 15 of gestation. The dams were sacrificed on day 22. The dams were weighed on days 1, 6 through 15 and 22. At sacrifice, the number of corpora lutea, and for the foetuses their weights, their viability and external and visceral malformations were recorded. In the high dose group, 5 dams died, 5 were not pregnant at sacrifice and one dam had resorbed all seven foetuses. Body weight gain in this group was significantly reduced. Foetuses of the high dose group (only 2 litters) showed reduced viability, reduced weight, increased incidence of resorptions and increased ossification anomalies of the sternbrae and upper skull. However, the figures were not statistically significant. No significant effects were recorded in the dams below 1000

mg/kg b.w. In the 500 mg/kg b.w.-group, the foetuses had an increased number of missing or unossified sternebrae, which was significant at foetus level, but not at litter level. No significant effects were seen at the two lowest dose levels. (Khera et al. 1979)

4.5.3 Dermal contact

No data were found.

4.6 Mutagenic and genotoxic effects

4.6.1 *In vitro* studies

Several tests have been conducted *in vitro* in bacteria, yeast as well as in mammalian cells. The tests are summarised in Table 2 and 3 on the basis of information from IUCLID (2000) and CICAD (1999):

Table 2: Bacterial and yeast genotoxicity tests with biphenyl

| Species/test system (strains) | End-point | Concentration | Results with/without metabolic activation | Reference |
|---|---------------------------|---------------------|---|---|
| <i>S. typhimurium</i> (TA97a, TA98, TA100, TA102) | Reverse mutation | 0- 500 µg/plate | - / - | Fujita et al. (1985) |
| <i>S. typhimurium</i> (TA92, TA94, TA98, TA100, TA1535, TA1537) | Reverse mutation | Up to 5000 µg/plate | - / n.a. | Ishidate et al. (1984) |
| <i>S. typhimurium</i> (TA98, TA100, TA1535, TA1538) | Reverse mutation | 4-2500 µg/plate | - / 0 | Purchase et al. (1978) |
| <i>S. typhimurium</i> (TA98, TA100, TA1532, TA1535, TA1538, TA2636) | Reverse mutation | 0.1-500 µg/plate | - / - | Pagano et al. (1983) |
| <i>S. typhimurium</i> (TA98, TA100, TA1535, TA1537, TA1538) | Reverse mutation | No data | - / - | Probst et al. (1981) |
| <i>S. typhimurium</i> (TA97, TA98, TA100) | Reverse mutation | 1-100 µg/plate | - / - | Brams et al. (1987) |
| <i>S. typhimurium</i> (TA98, TA100, TA1535, TA1537, TA1538) | Reverse mutation | 0.1-1000 µg/ml | - / - | Cline & McMahon (1977) |
| <i>Escherichia coli</i> (WP2, WP2 uvrA) | Gene mutation | 0.1-1000 µg/ml | - / - | Cline & McMahon (1977) |
| <i>E. coli</i> (PQ37) | DNA damage | 2.4-154 µg/ml | - / - | Brams et al. (1987) |
| <i>Bacillus subtilis</i> / recombination assay | DNA damage | No data | n.a./ - | Kawachi et al. (1980) |
| <i>Saccharomyces cerevisiae</i> (D7) / mitotic recombination | Gene mutation/ conversion | ≤ 154 µg/ml | + / + | Pagano et al. (1983) |
| <i>S. cerevisiae</i> (D3)/mitotic recombination | Gene conversion | No data | - / - | Waters et al. (1982) Zimmerman et al. (1984) |

+: positive result

-: negative result

n.a.: not assessed

Table 3: Mutagenicity tests with biphenyl in mammalian cells

| Species/test system (strains) | End-point | Concentration | Results with/without metabolic activation | Reference |
|--|---------------------------|--------------------------------------|---|--|
| Chinese hamster cells | Gene mutation | 0-100 µg/ml | - / - | Glatt et al. (1992) |
| Mouse lymphoma L5178Y TK ^{+/+} cells / mouse lymphoma assay | Gene mutation | 0-61 µg/ml | (+) / - | Wangenheim & Bolcsfoldi (1988) |
| Chinese hamster lung fibroblasts | Chromosomal aberration | No data | n.a. / - | Kawachi et al. (1980) |
| Chinese hamster lung fibroblasts | Chromosomal aberration | 0-60 µg/ml, respectively 0-125 µg/ml | n.a. / - | Ishidate & Odashima (1977) Sofuni et al. (1985) |
| Chinese hamster lung fibroblasts | Chromosomal aberration | 0-20 µg/ml | + / - | Sofuni et al. (1985) |
| Chinese hamster cells (DON) | Chromosomal aberration | 15.4 –154 µg/ml | n.a. / - | Abe & Sasaki (1977) |
| Chinese hamster cells (CHL) | Sister chromatid exchange | No data | n.a. / - | Kawachi et al. (1980) |
| Chinese hamster cells (DON) | Sister chromatid exchange | 15.4-154 µg/ml | n.a. / - | Abe & Sasaki (1977) |
| Mouse lymphoma L5178Y cells TK ^{+/+} / alkaline unwinding assay | DNA strand breaks | 0-231 µg/ml | + / - | Garberg et al. (1988) |
| Primary rat hepatocytes | Unscheduled DNA synthesis | 0.077-154.2 µg/ml | - | Probst et al. (1981) |
| Primary rat hepatocytes | Unscheduled DNA synthesis | 0.002-154.2 µg/ml; resp. 15.4 µg/ml | - | Brouns et al. (1979), Williams (1978) |
| Human lung fibroblasts (WI-38 cells) | Unscheduled DNA synthesis | No data | - / - | Water et al. (1982) |
| Human fibroblasts / nick translation assay | DNA damage | 15.4 µg/ml | n.a. / - | Snyder & Matheson (1985) |

+: positive result
 -: negative result
 n.a.: not assessed

4.6.2 *In vivo* studies

Sprague-Dawley rats were exposed by inhalation to 64 or 320 mg biphenyl/m³, 5 days/week, 7 hours/day for 30 days (20 exposures). No significant increase in chromosomal aberrations was observed. The validity of the study is questioned due to lack of data on harvesting times or on whether the bone marrow was reached by the chemical and to the low number of cells examined (50 cells/animal). (Dow Chemical Co. 1976 – quoted from IUCLID 2000 and CICAD 1999).

No chromosomal aberrations are reported from rat bone marrow in a cytogenetic assay. No details on doses, application route or harvesting technique were available (Kawachi et al. 1980 – quoted from IUCLID 2000 and CICAD 1999).

4.7 Carcinogenic effects

4.7.1 Inhalation

No information was found.

4.7.2 Oral intake

Fifteen albino rats/sex/group were exposed through the diet to 0, 0.001, 0.005, 0.01, 0.05, 0.1, 0.5, or 1% biphenyl (corresponding to ca. 0, 0.75, 3.75, 7.5, 37.5, 75, 375 or 750 mg/kg b.w./day) for 2 years. General findings are described under point 4.4.2. No tumours were found in the liver of controls or experimental animals. Incidences of other tumour types are shown in Table 4.

Table 4: Incidence and location of tumours in rats following 2 years dietary exposure to biphenyl

| | Bladder | | Lung | | Breast | Hypophysis | | Adrenal | | Uterus | Other | |
|----------|---------|-----|------|------|--------|------------|------|---------|------|--------|-------|-----|
| | F | M | F | M | F | F | M | F | M | F | F | M |
| Controls | 1/9 | 2/9 | | | 3/9 | 2/7 | 1/7 | | 2/7 | 2/9 | | |
| 0.001% | | 2/8 | 1/6 | | 3/6 | 3/5 | 2/7 | | 1/6 | 1/6 | | 1/9 |
| 0.005% | | | | | 2/6 | | 2/6 | | | 1/6 | | |
| 0.01% | | 1/9 | | 1/11 | 4/11 | 3/10 | 1/8 | | | 4/11 | | |
| 0.05% | | | 2/5 | 2/13 | 1/5 | 1/3 | 1/12 | 2/5 | 1/13 | | | |
| 0.1% | | 1/9 | 1/5 | 1/9 | | | 1/8 | | 1/9 | 2/5 | | |
| 0.5% | | 1/2 | | | 1/5 | 1/3 | | 2/5 | | | | |
| 1.0% | | 1/2 | | | | | | | | | | 1/2 |

F: females

M: males

No dose-response relationship could be established for any tumour type. Bladder tumours varied from local papillary proliferation of the epithelium to protruding tumours. However, the author evaluated that none of them were clearly malignant. Five out of 8 lung tumours were malignant, however, all five occurred at the 3 lowest doses and no lung tumours occurred at the two highest dose levels. Breast, hypophysis and adrenal tumours were benign, while 1 out of 10 uterine tumours at the 1.0% level was malignant. One pancreas carcinoma occurred in a control female and a proliferative lesion in fatty tissue occurred in the high dose males. (Ambrose et al. 1960).

A 2-year study was performed according to standard protocols with F344/DuCrj-rats, using diets containing 0, 0.05, 0.15 or 0.45% biphenyl (corresponding to 0, 38, 113 or 338 mg/kg b.w./day). As described in section 4.4.2, blood parameters were affected in a dose-related way. Hyperplasia of epithelium in the urinary bladder, the urethra and the renal pelvis and occurrence of calculi is described in 4.4.2. In the high dose males, there were significant increases in bladder transitional cell papilloma (10/50) and carcinoma (24/50) as well as a slight increase in squamous cell papilloma (1/50) and carcinoma (1/50). No tumours occurred in the urinary bladder of high dose females or in any other treatment or control group of either sex. (Japan Bioassay Research Centre 1996 – quoted from CICAD 1999).

Mice (Strains: C57/BL/6 X C3H/Anf and C57BL X AKR) were treated with 2.5 mg biphenyl/kg b.w./day by stomach tube for 3 weeks, followed by dietary treatment with 0.05% (equivalent to 71 mg/kg b.w./day) for 17 weeks. The animals were sacrificed after 18 months and examined macroscopically and microscopically. There was no significant increased incidence in any tumour in the biphenyl-treated animals compared to controls. (Innes et al. 1969 – quoted from IUCLID).

Crj:BDF₁-mice were given diets containing 0, 0.07, 0.2 or 0.6 % biphenyl/kg (corresponding to 0, 100, 300 or 900 mg/kg b.w./day) for 104 weeks. Effects on body weights, respiratory epithelium, liver, blood parameters and degenerative changes in the kidney are described in section 4.4.2. In females of the treated groups, there was a significant, but not concentration-dependent increase in liver tumours (hepatocellular adenomas and carcinomas). No significant differences between treated and control animals were seen as to liver tumours in males or tumours in the bladder or kidney. (Japan Bioassay Research Centre 1996 – quoted from CICAD 1999).

4.7.2.1 Tumour promotion studies

18 male F344-rats were administered drinking-water containing 0.05% of the initiator *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine (BBN) for 4 weeks, followed by 0.5% biphenyl in the diet (estimated to correspond to 375 mg/kg b.w./day) for 32 weeks. Twenty-four male rats were only exposed to BBN, and 21 males to biphenyl only. The animals were then sacrificed and the bladders were examined histopathologically. Rats treated with biphenyl-only showed no hyperplasia, papillomas or carcinomas. 25% of the BBN-only treated animals had hyperplasia, 12% papillomas, but no carcinomas occurred. As regards rats treated with both substances, 94% had hyperplasia, 83% papillomas and 61% carcinomas. On this basis, the authors concluded that biphenyl was a tumour promoter. (Kurata et al. 1986 – quoted from CICAD 1999).

In another rat study investigating the tumour-promoting potential of biphenyl, male Wistar rats were administered 0.1% *N*-ethyl-*N*-hydroxyethylnitrosamine (EEN) in the diet for 2 weeks and/or 0, 0.125 or 0.5% biphenyl in the diet for 34 weeks. No dysplastic foci or renal cell tumours were seen. However, 0.5% biphenyl alone or in combination with EEN did cause an increase in stones of the kidneys, urethra and bladder. (Shiraiwa et al. 1989 – quoted from CICAD 1999).

A study on tumour promotion used male B6C3F₁-mice administered drinking water containing 0.05% of the initiator *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine (BBN) for 4 weeks and/or diets containing 1% biphenyl (corresponding to 1500 mg/kg b.w./day) for 32 weeks. Histopathology of the urinary bladder revealed no carcinomas in any groups. In the biphenyl-only treated group, there was 10% hyperplasia and 10% papillary or nodular dysplasia. BBN-only treated mice had 60% hyperplasia and 10% papillary or nodular dysplasia, while the combined group had 70% hyperplasia and 5% papillary or nodular dysplasia in the urinary bladder. The groups treated with biphenyl, with and without BBN pre-treatment showed incidences of interstitial nephritis of 65 and 50%, respectively. (Tamano et al. 1993 – quoted from CICAD 1999).

4.7.3 Dermal contact

No skin papillomas or carcinomas were found in a skin painting study in Sutter mice treated with 25 µl of a solution containing 20% biphenyl in benzene twice weekly for 15 weeks after initiator treatment with a single dermal application of 0.3% of a 9,10-dimethyl-1,2-benzanthracene solution in benzene or in mice used as control group. No information was given on mice treated with biphenyl without initiator treatment. (Boutwell 1959 – quoted from CICAD 1999 and IUCLID 2000).

A nuclear enlargement assay was conducted in TO-mice by applying 0.1 ml per animal of a solution containing 10.5 mM/ml (corresponding to 0.162 mg biphenyl) in methyl ethyl ketone with 0.1% croton oil twice daily for 3 days. According to the authors, there is a close correlation between capacity to induce epidermal nuclear enlargement and topical carcinogenicity. Biphenyl did not produce nuclear enlargement. (Ingram & Grasso 1985 – quoted from IUCLID 2000).

5 Regulations

5.1 Ambient air

-

5.2 Drinking water

-

5.3 Soil

-

5.4 Occupational Exposure Limits

Denmark: 0.2 ppm (1 mg/m³) (At 2005)

ACGIH: 0.2 ppm (ACGIH 2001)

Germany: -

5.5 EU-Classification

Biphenyl is classified for irritative effects (Xi;R36/37/38 – irritating to eyes, respiratory system and skin) and for environmental toxicity (N;R50/53 – very toxic to aquatic organisms, may cause long-term effects in the aquatic environment) (MM 2002).

5.6 IARC

-

5.7 US-EPA

-

6 Summary and evaluation

6.1 Description

Biphenyl is a colourless solid with a flaky appearance and a geranium-like odour. Its melting point is 70°C. It is insoluble in water.

6.2 Environment

Biphenyl occurs naturally in coal tar, crude oil and natural gas. Citrus fruit or wood preserving facilities, municipal waste disposal sites, exhaust from vehicle traffic and from heating facilities are also source of environmental exposure. Levels in ambient air range from 1 to 100 ng/m³. The atmosphere appears to be the main compartment for biphenyl. Biphenyl is degraded by hydroxyl radicals with a half-life of about 2 days. In soil, biphenyl is aerobically degraded by microbial organisms. The mobility in soil is low. Biphenyl levels in surface water are usually below 500 ng/cm³. Water degradation data were not found.

6.3 Human exposure

The general population is exposed to biphenyl through air pollution from vehicle traffic and heating facility exhaust. Indoor biphenyl exposure is higher, due to cigarette smoking and heating facilities or nearby gas stations exhaust.

Skin exposure occurs from products treated with or produced from coal tar and crude oil such as creosote-treated wood or from biphenyl treated citrus fruits.

Exposure through the food primarily includes treated citrus fruits. Tap water has a low contamination level of biphenyl.

6.4 Toxicokinetics

High urinary excretion of biphenyl (92% of oral dose) indicates high absorption by the oral route. No data on absorption through inhalation was available. Biphenyl is oxidised to hydroxybiphenyls, of which 4-hydroxybiphenyl is the major metabolite in different animal species. Also di- and trihydroxybiphenyl have been demonstrated in urine of rats. Glucuronic conjugation of the phenolic metabolites occurs extensively before urinary excretion, which accounts for 92% of an oral dose administered to rats. Excretion of biphenyl through faeces accounts for a minor part, mostly as the unchanged compound.

6.5 Human toxicity

6.5.1 Single dose toxicity

No information on systemic toxicity of biphenyl following single exposure was found.

6.5.2 Irritation

Inhalation of 19.3-25.7 mg/m³ of a mixture of biphenyl(26.5%) with biphenyl ether was irritating to eyes, nose and throat.

The respiratory irritation threshold to biphenyl was reported to be 7.5 mg/m³ (no information on exposure conditions reported).

6.5.3 Sensitisation

A handbook quotation on the sensitising potential of biphenyl was not supported by any data and is considered erroneous.

6.5.4 Repeated dose toxicity

Occupational exposure by inhalation to biphenyl in impregnating paper production caused irritation of the respiratory tract and central and peripheral nervous system depression. Serious liver atrophy and fatty changes were also reported following inhalation, dermal and or oral exposure of biphenyl, although mixed exposure with tri- and tetrachloroethylene could not be excluded. One case was fatal.

6.5.5 Toxicity to reproduction

No data were found.

6.5.6 Mutagenic and genotoxic effects

No data were found.

6.5.7 Carcinogenic effects

No evidence of carcinogenicity was found in a case study of occupational exposure to biphenyl over 10 years.

6.6 Animal toxicity

6.6.1 Single dose toxicity

Rats exposed to 960 and 3740 mg/m³ showed severe irritation of the trachea and lung oedema. Inhalation of 275 mg biphenyl/m³ caused reversible respiratory tract irritation and lung congestion in mice.

Oral LD₅₀-values were reported to range from 2400-5040 mg/kg b.w. for rats. Rabbits LD₅₀-values were in the same range, while guinea pigs appear to be less sensitive to biphenyl.

A dermal LD₅₀-value of 2500 mg/kg b.w was reported in rabbits.

6.6.2 Irritation

Solid biphenyl was reported not to be irritating to the intact or abraded skin of rabbits, while intradermal injections to guinea pigs of a solution in corn oil produced inflammation. Slight eye irritation was reported from a test in one rabbit, and another test reported no irritation from a 17% biphenyl containing mixture.

6.6.3 Sensitisation

No conclusion could be made on the sensitising potential of biphenyl because of severe inflammation of the skin at the intradermal injection sites in a guinea pig maximisation test.

6.6.4 Repeated dose toxicity

In rats, inhalation of 40 or 300 mg biphenyl/m³ as a dust over 6-8 weeks caused severe inflammatory reaction in the respiratory tract and in the lung. The NOAEC was 5 mg/m³. Mice appear to be more a sensitive species, as a similar experiment in this species resulted in the same type of effects, but with 5 mg/m³ as a LOAEC. No adverse effects were seen in rabbits in a similar test. In mice, exposure for 13 weeks to 160 and 320 mg/m³ biphenyl resulted in hyperaemia in the lung and hyperplasia of the tracheal epithelium; the lowest concentration of 160 mg/m³ can be regarded as a LOAEC. However, the effects could be due to the temperature of the aerosol containing air, as effects were also seen in the controls.

Several oral studies have been conducted in rats (males and females of Wistar, Fischer 344 and unspecified strains) with duration from 3 to 104 weeks. Polyuria, increased urine turbidity and occurrence of precipitates turning to stone were reported together with elevated DNA-synthesis and hyperplasia of the bladder epithelium. Kidney effects ranged from dilated tubules and renal cysts to hyperplasia and calcification of the epithelium probably due to the acidity of urine and, in the long-term studies, the formation of calculi in the kidney. The lowest LOAEL for effects in the bladder and the kidneys was 188 mg/kg b.w./day in a 75 week- study in rats.

One recent oral 2 year-study in F344 rats conducted in accordance to standard protocols revealed dose-related haemoglobin and haematocrit depression. The LOEL for these effects was 38 mg/kg b.w./day.

In a dermal study using 500 mg biphenyl/kg b.w. on rabbit skin over 4 weeks, no skin effects were seen, but effects on the spleen were reported including loss of pulp cells and neutrophilic leucocyte infiltration. In another study over 6 weeks, not reporting the dose applied, biphenyl did not produce irritation, sensitisation or histopathological changes in rabbits.

6.6.5 Toxicity to reproduction

No effects on fertility were seen in a two-generation study in rats using up to 375 mg/kg b.w./day. In a three-generation study in rats, 750 mg/kg b.w./day caused reduction in fertility, litter size and growth rates; no further information was available from this study. The NOAEL for effects on reproduction was 75 mg/kg b.w./day. No histopathological changes of the reproductive organs were reported in rats or mice fed up to 450 and 675 mg/kg b.w./day, respectively, for two years.

In an oral developmental study in rats with doses from 125 to 1000 mg biphenyl/kg b.w./day, the high dose was severely toxic to the dams and offspring. At 500 mg/kg b.w./day, no significant effects were seen in the dams, while missing or unossified sternebrae were reported in the foetuses. This effect was not significant at litter level, but only at foetus level. The NOAEL for developmental effects is considered to be 250 mg/kg b.w./day.

6.6.6 Mutagenic and genotoxic effects

Biphenyl was negative in bacterial assays and positive in a gene mutation/ conversion assay in yeast with and without metabolic activation, while another yeast gene conversion assay was negative. In mammalian cells, biphenyl was negative in gene mutation tests, UDS tests, DNA damage and chromosome aberration assays, except for one chromosomal aberration assay in CHO-cells and one DNA strand-break assay in mouse lymphoma cells, which were positive with metabolic activation. Two negative *in vivo* chromosome aberration studies are available. However, their quality is questionable and the *in vivo* mutagenicity of biphenyl cannot be conclusively evaluated on this background. However, the weight of evidence from the available studies indicates that biphenyl is not a mutagen.

6.6.7 Carcinogenic effects

The incidence of tumours (benign and malignant) in the urinary bladder was increased in male F344-rats exposed to 338 mg biphenyl/kg b.w. in the diet for 2 years. Female F344-rats did not show this effect, nor did male or female BDF₁-mice. Biphenyl also showed tumour promoting effect with respect to bladder tumours development in male rats, but not in male mice. The mechanism for tumour formation in the bladder may be related to the formation of calculi in the bladder and consequent hyperplasia of the urothelium. Male rats are regarded to be more sensitive to this effect than female rats, mice and humans. However, although biphenyl did not produce tumours in female rats, there was an increase in occurrence of calculi and hyperplasia at the high dose although not as pronounced as in the males. A potential of biphenyl to produce bladder tumours in female rat cannot be ruled out.

In mice, a slight increase in liver tumour incidence was seen in the females, although the finding was not dose-dependent.

6.7 Critical effect and NOAEL

The critical effect in humans following exposure to biphenyl by inhalation is considered to be effects observed in the respiratory tract and the lungs. An irritation threshold of 7.5 mg/m³ has been reported for humans. However this value is a table value, and no details on exposure duration or whether the substance was present as vapour or aerosol are available. Repeated inhalation studies in animals have also shown respiratory tract irritation to biphenyl (dust on celite) with a NOAEC of 5 mg/m³ (the lowest concentration tested) in rats and a LOAEC of 5 mg/m³ (the only concentration tested) in mice. At the higher concentrations tested in rats (40, 300 mg/m³), severe inflammatory bronchopulmonary changes were observed as well. Two of the 12 mice exposed to 5 mg/m³, which died, also showed inflammatory bronchopulmonary changes.

For the purpose of estimating a health based quality criterion in air, 5 mg/m³ is considered as a LOAEC for effects in the respiratory tract and the lungs. The inha-

lation studies, have been chosen despite their limitations instead of the oral toxicity studies because the effects observed in the oral studies are not considered as being relevant for the assessment of inhalation of biphenyl. In the inhalation studies, biphenyl was administered as dust on celite, a diatomaceous earth product; it is considered that effects will not be observed following inhalation of biphenyl as a vapour at lower concentrations than 5 mg/m^3 .

7 Quality criterion in air

The quality criterion in air QC_{air} is calculated based on a LOAEC of 5 mg/m^3 for effects in the respiratory tract and the lungs:

$$\begin{aligned} QC_{\text{air}} &= \frac{\text{LOAEC}}{UF_{\text{I}} * UF_{\text{II}} * UF_{\text{III}}} = \frac{5 \text{ mg/m}^3}{10 * 10 * 10} \\ &= 0.005 \text{ mg/m}^3 \end{aligned}$$

The uncertainty factor UF_{I} accounting for interspecies variability is set to 10, assuming that humans are more sensitive than animals. The UF_{II} accounting for intraspecies variability is set to 10 reflecting the range in biological sensitivity within the human population. The UF_{III} is set to 10 because of using a LOAEC instead of a NOAEC and to take into account the limitations of the available inhalation studies.

A quality criterion of 0.005 mg/m^3 has been calculated.

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Evaluation of health hazards by exposure to Biphenyl and proposal of a health-based quality criterion for ambient air

The Danish Environmental Protection Agency has requested an evaluation of health hazards by exposure to biphenyl. This resulted in 2006 in the present report which includes a health-based quality criterion for the substance in ambient air.



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