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Concise International Chemical Assessment Document 6

BIPHENYL

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The **International Programme on Chemical Safety (IPCS)**, established in 1980, is a joint venture of the United Nations Environment Programme (UNEP), the International Labour Organisation (ILO), and the World Health Organization (WHO). The overall objectives of the IPCS are to establish the scientific basis for assessment of the risk to human health and the environment from exposure to chemicals, through international peer review processes, as a prerequisite for the promotion of chemical safety, and to provide technical assistance in strengthening national capacities for the sound management of chemicals.

The **Inter-Organization Programme for the Sound Management of Chemicals (IOMC)** was established in 1995 by UNEP, ILO, the Food and Agriculture Organization of the United Nations, WHO, the United Nations Industrial Development Organization, the United Nations Institute for Training and Research, and the Organisation for Economic Co-operation and Development (Participating Organizations), following recommendations made by the 1992 UN Conference on Environment and Development to strengthen cooperation and increase coordination in the field of chemical safety. The purpose of the IOMC is to promote coordination of the policies and activities pursued by the Participating Organizations, jointly or separately, to achieve the sound management of chemicals in relation to human health and the environment.

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TABLE OF CONTENTS

FOREWORD 1

1. EXECUTIVE SUMMARY 4

2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES 6

3. ANALYTICAL METHODS 6

4. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE 6

5. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION 7

6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE 8

6.1 Environmental levels 8
6.2 Human exposure 8

7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS 9

8. EFFECTS ON LABORATORY MAMMALS AND *IN VITRO* TEST SYSTEMS 9

8.1 Single exposure 9
8.2 Irritation and sensitization 10
8.3 Short-term exposure 10
8.3.1 Oral exposure 10
8.3.2 Inhalation exposure 10
8.3.3 Dermal exposure 10
8.4 Long-term exposure 10
8.4.1 Subchronic exposure 10
8.4.1.1 Oral exposure 10
8.4.1.2 Inhalation exposure 12
8.4.2 Chronic exposure and carcinogenicity 12
8.4.2.1 Tumour promotion 13
8.5 Genotoxicity and related end-points 15
8.6 Reproductive and developmental toxicity 15
8.7 Immunological and neurological effects 16

9. EFFECTS ON HUMANS 16

10. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD 17

10.1 Aquatic environment 17
10.2 Terrestrial environment 17

11. EFFECTS EVALUATION 18

11.1 Evaluation of health effects 18
11.1.1 Hazard identification and dose–response assessment 18
11.1.2 Criteria for setting guidance values for biphenyl 19
11.1.3 Sample risk characterization 19
11.2 Evaluation of environmental effects 19

12. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES 20

13. HUMAN HEALTH PROTECTION AND EMERGENCY ACTION 20

13.1 Advice to physicians 20
13.2 Health surveillance advice 20
13.3 Spillage 21

14. CURRENT REGULATIONS, GUIDELINES, AND STANDARDS 21

INTERNATIONAL CHEMICAL SAFETY CARD 22

REFERENCES 24

APPENDIX 1 — SOURCE DOCUMENTS 28

APPENDIX 2 — CICAD PEER REVIEW 28

APPENDIX 3 — CICAD FINAL REVIEW BOARD (Brussels, Belgium) 29

APPENDIX 4 — SPECIALIZED CICAD PEER REVIEW 30

APPENDIX 5 — CICAD FINAL REVIEW BOARD (Washington, DC) 30

RÉSUMÉ D'ORIENTATION 32

RESUMEN DE ORIENTACIÓN 35

FOREWORD

Concise International Chemical Assessment Documents (CICADs) are the latest in a family of publications from the International Programme on Chemical Safety (IPCS) — a cooperative programme of the World Health Organization (WHO), the International Labour Organisation (ILO), and the United Nations Environment Programme (UNEP). CICADs join the Environmental Health Criteria documents (EHCs) as authoritative documents on the risk assessment of chemicals.

CICADs are concise documents that provide summaries of the relevant scientific information concerning the potential effects of chemicals upon human health and/or the environment. They are based on selected national or regional evaluation documents or on existing EHCs. Before acceptance for publication as CICADs by IPCS, these documents undergo extensive peer review by internationally selected experts to ensure their completeness, accuracy in the way in which the original data are represented, and the validity of the conclusions drawn.

The primary objective of CICADs is characterization of hazard and dose–response from exposure to a chemical. CICADs are not a summary of all available data on a particular chemical; rather, they include only that information considered critical for characterization of the risk posed by the chemical. The critical studies are, however, presented in sufficient detail to support the conclusions drawn. For additional information, the reader should consult the identified source documents upon which the CICAD has been based.

Risks to human health and the environment will vary considerably depending upon the type and extent of exposure. Responsible authorities are strongly encouraged to characterize risk on the basis of locally measured or predicted exposure scenarios. To assist the reader, examples of exposure estimation and risk characterization are provided in CICADs, whenever possible. These examples cannot be considered as representing all possible exposure situations, but are provided as guidance only. The reader is referred to EHC 170[1] for advice on the derivation of health-based guidance values.

While every effort is made to ensure that CICADs represent the current status of knowledge, new information is being developed constantly. Unless otherwise stated, CICADs are based on a search of the scientific literature to the date shown in the executive summary. In the event that a reader becomes aware of new information that would change the conclusions drawn in a CICAD, the reader is requested to contact IPCS to inform it of the new information.

Procedures

The flow chart shows the procedures followed to produce a CICAD. These procedures are designed to take advantage of the expertise that exists around the world — expertise that is required to produce the high-quality evaluations of toxicological, exposure, and other data that are necessary for assessing risks to human health and/or the environment.

The first draft is based on an existing national, regional, or international review. Authors of the first draft are usually, but not necessarily, from the institution that developed the original review. A standard outline has been developed to encourage consistency in form. The first draft undergoes primary review by IPCS to ensure that it meets the specified criteria for CICADs.

The second stage involves international peer review by scientists known for their particular expertise and by scientists selected from an international roster compiled by IPCS through recommendations from IPCS national Contact Points and from IPCS Participating Institutions. Adequate time is allowed for the selected experts to undertake a thorough review. Authors are required to take reviewers' comments into account and revise their draft, if necessary. The resulting second draft is submitted to a Final Review Board together with the reviewers' comments.

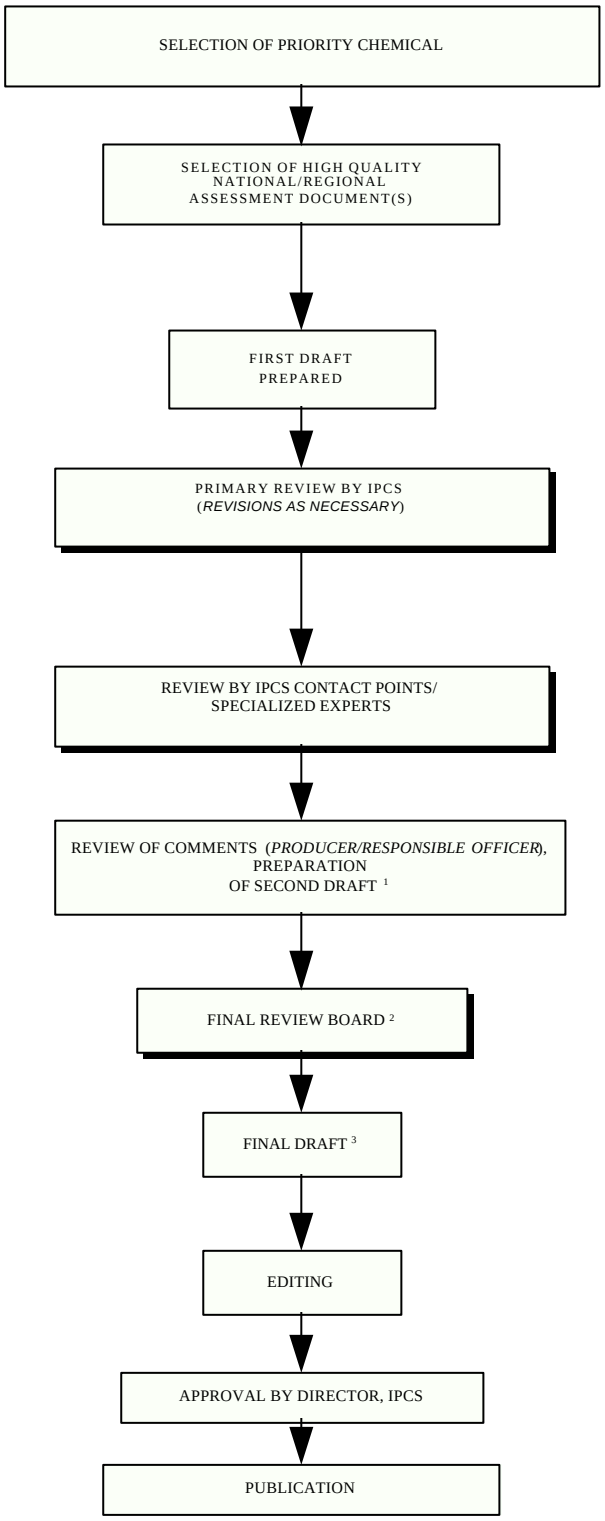
The CICAD Final Review Board has several important functions:

- to ensure that each CICAD has been subjected to an appropriate and thorough peer review;
- to verify that the peer reviewers' comments have been addressed appropriately;
- to provide guidance to those responsible for the preparation of CICADs on how to resolve any remaining issues if, in the opinion of the Board, the author has not adequately addressed all comments of the reviewers; and
- to approve CICADs as international assessments.

Board members serve in their personal capacity, not as representatives of any organization, government, or industry. They are selected because of their expertise in human and environmental toxicology or because of their

[1] International Programme on Chemical Safety (1994) *Assessing human health risks of chemicals: derivation of guidance values for health-based exposure limits.* Geneva, World Health Organization (Environmental Health Criteria 170).

CICAD PREPARATION FLOW CHART



1 Taking into account the comments from reviewers.
2 The second draft of documents is submitted to the Final Review Board together with the reviewers' comments.
3 Includes any revisions requested by the Final Review Board.

experience in the regulation of chemicals. Boards are chosen according to the range of expertise required for a meeting and the need for balanced geographic representation.

Board members, authors, reviewers, consultants, and advisers who participate in the preparation of a CICAD are required to declare any real or potential conflict of interest in relation to the subjects under discussion at any stage of the process. Representatives of nongovernmental organizations may be invited to observe the proceedings of the Final Review Board. Observers may participate in Board discussions only at the invitation of the Chairperson, and they may not participate in the final decision-making process.

1. EXECUTIVE SUMMARY

This CICAD on biphenyl was prepared by the Fraunhofer Institute for Toxicology and Aerosol Research, Hanover, Germany, based principally on a review prepared by the German Advisory Committee on Existing Chemicals of Environmental Relevance (BUA, 1990) as well as a supplementary report (BUA, 1994) to assess the potential effects of biphenyl on humans and the environment. The source documents and a description of their review processes are presented in Appendix 1. A comprehensive literature search of several online databases to June 1996 was also conducted to identify any additional data. Additional information identified during review by contact points and consideration by the Final Review Board (Brussels, Belgium) has also been incorporated into this CICAD. Information on the peer review of this CICAD is presented in Appendix 2. This CICAD was given provisional approval as an international assessment at a meeting of the Final Review Board held in Brussels, Belgium, on 18–20 November 1996. Participants at the Brussels Final Review Board meeting are listed in Appendix 3. Following the incorporation of data related to the carcinogenicity of this substance from a recently completed 2-year carcinogenicity bioassay, the revised document was subjected to two rounds of written peer review. In addition, that part of the document dealing specifically with the human health assessment (i.e. section 11.1) was reviewed at a meeting held at the National Center for Environmental Assessment, US Environmental Protection Agency, in Washington, DC (USA), on 7 December 1998. Individuals contributing to the additional specialized reviews of this CICAD are listed in Appendix 4. This CICAD was approved as an international assessment at a meeting of the Final Review Board held in Washington, DC (USA), on 8–11 December 1998. Participants at the Washington Final Review Board meeting are listed in Appendix 5. The International Chemical Safety Card (ICSC 0106) produced by the International Programme on Chemical Safety (IPCS, 1993) has also been reproduced in this document.

Biphenyl (CAS No. 92-52-4), an aromatic hydrocarbon, is a colourless solid at room temperature. It is used as an intermediate in the production of a variety of compounds (e.g. emulsifiers, optical brighteners, crop protection products, plastics), as a heat transfer medium in heating fluids, as a dyestuff carrier for textiles and copying paper, as a solvent in pharmaceutical production, and in the preservation of citrus fruits.

Biphenyl occurs naturally in coal tar, crude oil, and natural gas. Anthropogenic sources of environmental exposure include production and processing plants, citrus fruit or wood preserving facilities, and municipal waste disposal sites. Biphenyl is formed during the incomplete combustion of mineral oil and coal and is present in the exhaust gases of vehicle traffic and in exhaust air from residential and industrial heating devices. In ambient air, typical concentrations of biphenyl range from 1 to 100 ng/m^3. Levels in indoor air are higher (100–1000 ng/m^3), likely as a result of cigarette smoke and emissions from heating devices or nearby garages. In measurements conducted in the 1970s, levels of biphenyl in tap-water were usually below 5 ng/litre. More recent data were not identified. In surface waters, concentrations are typically below 500 ng/litre. In sediment, soil, and biota, biphenyl was measured only in the direct vicinity of industrial plants and waste dumps.

Biphenyl volatilizes from aqueous solution and has a low water solubility. The main degradation pathway in the troposphere is the reaction with hydroxyl radicals, for which a mean half-life of approximately 2 days has been calculated. The substance is not expected to hydrolyse under environmental conditions. It is biodegradable under aerobic conditions. Based upon available data, biphenyl should be almost immobile in soil; the probability of infiltration into groundwater is low. In the food-chain important to humans, bioaccumulation can take place, specifically in plants; however, based upon the potential bioaccumulation of biphenyl, biomagnification of biphenyl in higher trophic levels of the aquatic or terrestrial food-chain is expected to be of minor importance.

Biphenyl is well absorbed through the gastrointestinal tract and presumably also via lung and skin. In those species examined, the metabolites of biphenyl, mainly 4-hydroxybiphenyl, are excreted rapidly and almost exclusively in the urine. The acute oral toxicity of biphenyl is moderate. It is non-irritating to skin and only slightly irritating to the eyes. There is no evidence of dermal sensitization. Toxicity studies with biphenyl after repeated exposure by inhalation are not adequate to establish a no-observed-effect level (NOEL) with confidence. Subchronic exposure by inhalation caused bronchopulmonary changes, whereas long-term toxicity studies following inhalation exposure were not identified in the literature.

In toxicological studies in which rodents have been administered diets containing biphenyl for various periods of time, effects on the urinary system have often been reported. A marked increase in the incidence of morphological (i.e. formation of calculi) and histopathological (e.g. hyperplasia, desquamation) effects has been observed within the urinary tract of male rats administered diets containing more than 2500 mg biphenyl/kg. An increase in the occurrence of calculi and squamous metaplasia within the urinary bladder of female rats has also been observed, but at a lower incidence than in males. In male mice, only 1 of 10 animals given a diet containing 10 000 mg biphenyl/kg (1500 mg/kg body

weight per day) for 32 weeks developed simple hyperplasia and papillary or nodular dysplasia of the urinary bladder. Effects on blood chemistry and haematological parameters have also been observed in animals administered biphenyl orally; these effects occur in male and female rats and mice at intakes lower than those associated with the development of effects in the urinary bladder of male rats administered biphenyl. For non-neoplastic effects, the lowest-observed-effect level (LOEL) was 38 mg/kg body weight per day, based upon the development of alterations in haematological parameters (i.e. decreased haemoglobin concentration and haematocrit) in rats fed diets containing 0, 500, 1500, or 4500 mg biphenyl/kg (reported intakes of 0, 38, 113, or 338 mg/kg body weight per day) for 2 years.

In vitro studies with bacteria have provided no evidence of mutagenic potential for biphenyl; with *Saccharomyces cerevisiae* D7, gene mutation and mitotic recombination were observed with or without metabolic activation. However, genetic toxicology testing in mammalian cells has produced positive results in the presence of metabolic activation and negative results in the absence of metabolic activation. In one inadequately documented and inadequately performed *in vivo* study, biphenyl did not induce chromosomal aberrations in the bone marrow of rats after exposure by inhalation. The results of *in vitro* studies indicate that biphenyl has mutagenic potential; in the absence of reassurance from reliable results from *in vivo* tests, it is assumed that exposure to biphenyl may be associated with a mutagenic risk.

In female mice, there were slight increases in the incidences of benign and malignant liver tumours in animals receiving biphenyl in the diet for 2 years. An increased incidence of bladder tumours was observed in male rats, but not in female rats or male and female mice, administered diets containing high levels of biphenyl. There have been suggestions that the formation of such bladder tumours may be linked to the regenerative hyperplasia of the urinary epithelium, caused by the abrasion and damage to the urothelium that are produced by calculi formed within the urinary tract only at very high levels of exposure; it has also been suggested that, because of anatomical and physiological differences, the sex- and species-specific development of bladder tumours in male rats receiving high doses of biphenyl might not be strictly relevant to humans exposed to lower levels. However, 1) observations of an increased incidence of histopathological effects and the formation of calculi within the urinary bladder, in the absence of bladder tumours, in female rats administered biphenyl for 2 years, 2) a lack of data identifying a direct association between calculi formation, regenerative hyperplasia of the urothelium, and the development of bladder tumours within individual male animals, and 3) the potential genotoxicity of biphenyl could suggest that the development of bladder tumours in the male rats may not have been entirely due to effects associated with the formation of calculi within the urinary bladder. This observation, as well as evidence of hepatocarcinogenicity in female mice, raises some concerns with respect to the potential carcinogenicity of biphenyl.

Available data on the reproductive toxicity of biphenyl are limited. Apart from results of a three-generation study in rats, in which adverse effects (decreased fertility, litter size, growth rate) were noted, there was no evidence that biphenyl induced reproductive or developmental effects.

Exposure to high levels of biphenyl vapours or dust at the workplace results in irritation of the eyes and inflammation of the respiratory tract. Long-term exposure for several years to high biphenyl concentrations (up to 128 mg/m^3) caused damage to the liver and persistent neuronal changes; direct skin contact may have played a part, in addition to uptake through the respiratory tract.

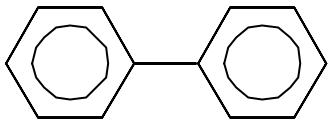
The available data on biphenyl levels in the general environment are limited, and the information is insufficient to permit a reasonable estimation of the intake of biphenyl. Inhalation (from polluted air and from the use of biphenyl-containing creosotes in wood preservation) and ingestion (from biphenyl's use as a preservative for citrus fruits) are possible sources of exposure.

Biphenyl has weak bactericidal and fungistatic properties. In toxicity studies on aquatic organisms of four trophic levels, the lowest no-observed-effect concentration (NOEC) reported for the most sensitive species (*Daphnia magna*) in chronic tests was 0.17 mg/litre. A predicted no-effect concentration (PNEC) of 1.7 ：g/litre can be calculated by applying an assessment factor of 10, considering ecotoxicological and environmental fate characteristics of the substance. Valid data on toxic effects on terrestrial organisms and ecosystems, which could be used for risk assessment, are not available.

Owing to the lack of data from other parts of the world, a sample risk assessment was performed for Germany. From concentrations measured in German rivers in the 1990s, the ratio of the predicted environmental concentration (PEC) to PNEC is calculated to be #0.29. A PEC/PNEC ratio of <1 indicates that a significant risk for the environment is not to be expected.

2. IDENTITY AND PHYSICAL/CHEMICAL PROPERTIES

Biphenyl (CAS No. 92-52-4; $C_{12}H_{10}$; 1,1'-biphenyl, diphenyl, phenylbenzene) has the following structural formula:



The chemical is an aromatic hydrocarbon with a peculiar, strong odour similar to that of geraniums (BUA, 1990). At room temperature, the substance is a colourless solid (melting point 69.2 °C). Because of its significant vapour pressure (4 Pa at 20 °C) and low water solubility (4.45 mg/litre at 20 °C), biphenyl shows considerable volatility from aqueous solutions (BUA, 1990). Its measured *n*-octanol/water partition coefficient (log K_{ow}) is between 3.88 and 4.04. The commercial product from the only German producer has a biphenyl content of 99.85%; named impurities are terphenyl (0.15%), sulfur (10–20 mg/kg), and benzene (1 mg/kg) (BUA, 1990). Additional physical/chemical properties are presented in the International Chemical Safety Card reproduced in this document.

3. ANALYTICAL METHODS

Biphenyl is usually measured in environmental media by capillary gas chromatography in combination with flame ionization or mass spectrometric detection (Malins et al., 1985; BUA, 1990; Hawthorne et al., 1992; Anklam & Mueller, 1994; Karanassios et al., 1994; Otson et al., 1994; Kostiainen, 1995). For aquatic samples, methods involving high-performance liquid chromatography with ultraviolet detection at 254 nm have also been described. The following enrichment techniques are used: solid-phase adsorption (Tenax material or XAD resins) with thermal desorption or liquid extraction for air samples, solid-phase adsorption (XAD resins) or liquid/liquid extraction (diethylether) for water samples, and liquid extraction (dichloromethane/ methanol, ethanol) for soil and biotic samples. The detection limits range from 0.1 to 5 ng/m^3 for air and from 0.01 to 8000 ng/litre for water. For sediment, a detection limit of 2 ：g/kg dry weight has been reported. Detection limits between 12 and 87 ：g/kg have been reported for levels of biphenyl in fish (Malins et al., 1985).

4. SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

Biphenyl occurs in varying concentrations in coal tar, crude oil (up to 0.4 mg/g oil), and natural gas (3–42 ：g/m^3) (BUA, 1990). Because of its natural occurrence in coal tar and crude oil, biphenyl has also been detected in products derived from these substances. The biphenyl content in coal tar-derived creosotes ranges between 0.2 and 1.6% (IARC, 1985; ATSDR, 1990; Collin & Hoeke, 1995). In the aromatic fraction of an unused lubricating oil sample, biphenyl was measured at a concentration of 1.5 mg/kg (Paschke et al., 1992).

Biphenyl is also produced from anthropogenic sources. In 1984, the estimated production capacities of biphenyl in the Federal Republic of Germany, in Western Europe, and throughout the world were approximately >6000, 30 000, and 80 000 t, respectively. In 1989, 2000–2500 t of biphenyl were produced in Germany, of which about 900 t were exported and 200–300 t sold domestically (BUA, 1990). Approximately 5000 t of biphenyl were manufactured in each of 1992 and 1993 in Japan (Anon., 1994–95).

Until the early 1970s, biphenyl was used principally as an intermediate in the production of polychlorinated biphenyls (PCBs). As the production, processing, distribution, and use of PCB compounds are now prohibited or restricted in many countries (e.g. USA, Germany, United Kingdom) (IRPTC, 1994), it is likely that previous production levels were much higher than those today. In 1984, the estimated use patterns of biphenyl worldwide were, as a final product: 35% in heat transfer medium in heating fluids, 20% as a dyestuff carrier for textiles, 5% as a solvent in pharmaceutical production, 5% as a dyestuff carrier for copying paper, and 5% as a preservative for citrus fruits; patterns of biphenyl use as an intermediate were: 10% each in emulsifiers and optical brighteners, 5% for crop protection products, and 5% for precursors and auxiliaries for plastics (BUA, 1990). At present in Germany, the use of biphenyl as a dyestuff carrier in textiles is minor.[1]

Although emissions from exhaust gases during production and processing of biphenyl and during the use of biphenyl-containing creosotes for wood preservation may be significant, available data were not identified. Biphenyl is also released into the atmosphere during the incomplete combustion of fossil fuels in motor vehicles (post-catalyst emission factor of 3.5 ：g/km; Siegl & Chladek, 1992), residential heating

[1] Personal communication from Verband d. Textilhilfsmittel-, Lederhilfsmittel-, Gerbstoff- und Waschrohstoff-Industrie e.V., Frankfurt/M., Germany, to Bayer AG, 1996.

(1.24 mg biphenyl/kg burnt coal; Engewald et al., 1993), and coal-burning power plants (with concentrations in flue gas up to 30 ：g/m^3; Yao & Xu, 1991; Wienecke et al., 1992) or foundries (qualitatively detected; Deusen & Kleinermanns, 1993).

In 1990, biphenyl was not detected in the effluent of the sewage plant of the German producer (detection limit 5 ：g/litre; weekly sampling). Based on a biphenyl concentration of <5 ：g/litre, a maximum annual release of 274 kg biphenyl can be calculated for this plant. No data are available from other producing or processing facilities. Biphenyl may also be released to surface water through the processing of coal tar (e.g. coking plants) and mineral oils (e.g. processing residual oils from pyrolysis in refineries) (BUA, 1990).[1] Based upon levels of biphenyl measured in sediment samples during the 1970s, this chemical has been released from various industrial wastewater outlets associated with a melting plant for iron alloys, a chemical factory, and an oil storage depot. Data were not available on releases of biphenyl from textile industries where the chemical is used as a dyestuff carrier, from wood preservation plants that use creosotes containing biphenyl, or from treated citrus fruits and their packaging materials contained in domestic waste sites. Concentrations of biphenyl between 0.016 ：g/kg and 1730 mg/kg have been measured in sewage sludge, which may be applied to arable land (BUA, 1990).

5. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

Based upon a Level II fugacity model (Mackay et al., 1992), the atmosphere appears to be the main target compartment (>90%) for biphenyl. Biphenyl's Henry's law constant indicates that it volatilizes from aqueous solutions. The calculated half-life for the photooxidative degradation of biphenyl by hydroxyl radicals in air is about 2 days (Atkinson & Aschmann, 1985; BUA, 1990; Atkinson & Arey, 1994). Reactions with tropospheric ozone and nitrate are expected to be of minor importance, with calculated half-lives of >80 days and >105 days, respectively. Data on the photodegradation of biphenyl in water are not available. Biphenyl is not expected to hydrolyse under environmental conditions.

In one reported standard test with activated sludge, according to Guideline 301C of the Organisation for Economic Co-operation and Development (OECD), a biochemical oxygen demand of 66% after 14 days' incubation was reported when non-adapted inoculum was used (CITI, 1992). Microbial populations from natural waters mineralize biphenyl; 100% degradation was observed after 4 days' incubation of biphenyl in river water (BUA, 1990). Numerous microorganisms isolated from soil, sediment, surface water, and groundwater samples have been shown to metabolize biphenyl (BUA, 1990; Bevinakatti & Ninnekar, 1992; Kiyohara et al., 1992; Nielsen & Christensen, 1994). Investigations on the anaerobic biodegradation of biphenyl were not identified.

Soil sorption coefficients (K_{oc}) based upon laboratory experiments and calculated values range from 1100 to 18 000 (BUA, 1990; Kishi & Hasimoto, 1991); from numerous literature data, Jeng et al. (1992) calculated a mean value of 4230. On the basis of these data, it is expected that biphenyl will be almost immobile in soil, with a low probability of groundwater infiltration. Volatilization from soil surfaces is significantly lower than that from aqueous media; however, no significant geoaccumulation of biphenyl is expected under aerobic conditions owing to its degradation by microbial organisms.

In static tests on the bioaccumulation of biphenyl in activated sludge conducted with several aquatic species (yeast, algae, molluscs, daphnia, and freshwater fish), bioconcentration factors (BCFs) ranging between 57 for the marine mussel *Mytilus edulis* (calculated on wet weight) (Donkin et al., 1991) and 540 for the green alga *Chlorella vulgaris* (based on dry weight) (Kotzias et al., 1980; Freitag et al., 1982) have been reported. With the exception of two tests, there was no information on whether equilibrium was reached before the determination of the BCF. The depuration of accumulated biphenyl was determined in one study. After a 24-h incubation in a static test system, the BCF at equilibrium (based on wet weight) for *Daphnia magna* was 473; depuration was dependent upon the temperature of the water. Twenty-four hours after being transferred to pure water, 53% of the accumulated biphenyl was depurated at 2–3 °C, whereas 88% was depurated at 22 °C (Zhang et al., 1983). Although the available data indicate a potential for bioaccumulation, evaporation, adsorption to soil/sediment, and degradation are expected to reduce the bioavailability of biphenyl. Therefore, bioaccumulation of the chemical should be of minor importance for aquatic organisms.

[1] Personal communication from Bayer AG to the GDCh-Advisory Committee on Existing Chemicals of Environmental Relevance, 1997.

6. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

6.1 Environmental levels

In 1985, concentrations of biphenyl in the air of an industrialized city in Finland ranged from 1.7 to 26.2 ng/m^3 (BUA, 1990). Similar concentrations were measured during the winter of 1988–89 in two US cities (12–119 ng/m^3; 30 ng/m^3 mean value; Hawthorne et al., 1992) and in 1992 in two Greek cities (all data below the detection limit of 5 ng/m^3; Karanassios et al., 1994).

The concentrations of biphenyl in the German parts of the Rhine River declined from a maximum of 1000 ng/litre in the 1970s (BUA, 1990) to levels below 500 ng/litre (the detection limit) in 1993–1995 (LWA, 1993–94).[1] Although levels in most of the German tributaries have remained below the detection limit (500 ng/litre), peak concentrations of 560 and 1600 ng/litre were reported in 1993 and 1994, respectively, for the highly polluted Emscher tributary (LWA, 1993–94); these elevated levels were attributed to the coking plants in this area.[2] In the USA, similar data for one river have been reported (Hites, 1973). In some German estuaries, biphenyl concentrations were significantly lower (1–5 ng/litre) (BUA, 1990).

During 1986–1989, biphenyl was detected at concentrations between 10 and 100 ng/litre in samples of groundwater obtained near Zagreb, in the former Yugoslavia, in the vicinity of a municipal landfill site. In a test well sunk 720 m from a heavily polluted river, the levels were about 10-fold lower (Ahel, 1991). Concentrations of biphenyl between 2 and 17 ng/litre have been measured in samples of snow and rain collected in Switzerland (BUA, 1990).

In river and estuarine sediments, biphenyl was detected at very high concentrations in the direct vicinity of industrial plants or waste dumps; concentrations ranged between 0.1 and 8 mg/kg, depending on the source. The highest concentrations were found near waste dump sites in the USA (Malins et al., 1985; BUA, 1990). Information on the occurrence of biphenyl in soils with no direct pollution was not identified. A maximum biphenyl concentration of 13 ：g/kg was found in soil samples collected near a pit for wastewater from oil production in New Mexico, USA (BUA, 1990).

Biphenyl has been found in fish collected from water contaminated with mineral oil; concentrations in liver samples were <25 ：g/kg dry weight (i.e. below the detection limit) and 13 620 ：g/kg fresh weight (Paasivirta et al., 1982; Malins et al., 1985).

6.2 Human exposure

The levels of biphenyl in indoor air may depend mainly on smoking habits (BUA, 1990). Concentrations of biphenyl are also elevated in homes having a source of oil and exhaust fumes nearby (e.g. gasoline station, parking garage) (Otson et al., 1994; Kostiainen, 1995). Monitoring data from Finnish (n = 50) (Kostiainen, 1995) and Canadian (n = 757) homes (Otson et al., 1994) have revealed average biphenyl concentrations in the range of 160–1000 ng/m^3, with a maximum concentration of 4700 ng/m^3 (Kostiainen, 1995). Biphenyl has been detected in floor dust collected from five of nine investigated Danish city halls (Wilkins et al., 1993). Assuming that 20 h are spent indoors (exposure to 160–1000 ng/m^3) and 4 h are spent outdoors (exposure to 30 ng/m^3) each day and that the inhalation volume and weight of the average adult are 22 m^3/day and 64 kg, respectively, the intake of biphenyl from air can be calculated from these data to range from 45 to 300 ng/kg body weight per day.

There is only limited intake of biphenyl from drinking-water. Although more recent data were not identified, concentrations of biphenyl in tap-water in various countries, such as Finland, Norway, Sweden, the USA, and Canada, were low (i.e. 0.1–5 ng/litre) in the 1970s (BUA, 1990). Based upon these data and assuming that the average adult (weighing 64 kg) consumes 2 litres of drinking-water per day, the estimated intake of biphenyl from drinking-water may range from 0.003 to 0.16 ng/kg body weight per day.

Food may contain biphenyl as a result of its use as a fungistatic agent for citrus fruits. In older studies with citrus fruits to which a biphenyl-containing wax had been applied, peels of treated fruits were found to contain up to 220 mg biphenyl/kg (whole fruit) and the pulp up to 3.9 mg/kg (whole fruit) (BUA, 1990); however, these levels were determined with a rather unspecific spectrophotometric method, which may have overestimated the biphenyl content. In a more reliable study with 6 grapefruits, 8 oranges, and 10 lemons obtained from Japanese markets, levels of biphenyl ranged from 17 to 123 mg/kg in the peel and from <0.01 (the detection limit) to 0.18 mg/kg (average 0.06 mg/kg pulp) in the edible parts of the fruit. In samples of lemon tea, levels of biphenyl were similar to those in the edible parts of the fruit (Isshiki et al., 1982). In a survey of foodstuffs

[1] Personal communication from the Northrhine-Westfalian Environmental Protection Agency to Bayer AG, 1996.

[2] Personal communication from Bayer AG to the GDCh-Advisory Committee on Existing Chemicals of Environmental Relevance, 1997.

conducted in Italy between 1988 and 1995, which included more than 70 types of food, biphenyl was detected in only one peach sample (detection limit not given) (Di Muccio et al., 1995). Based upon the average content of biphenyl in the pulp of citrus fruits of about 0.06 mg/kg (calculated from the concentrations measured by Isshiki et al., 1982), the intake from the consumption of the pulp of one biphenyl-preserved citrus fruit weighing about 120–400 g is calculated to be about 113–375 ng/kg body weight. An average intake of 64 ng biphenyl/kg body weight per day from food was calculated based upon the consumption of foodstuffs in Finland (Penttilae & Siivinen, 1996). The general population may also be exposed to biphenyl through contact with consumer products, such as creosote-preserved wood, textiles, copying papers, or pharmaceuticals, although quantitative data were not identified.

The intake of biphenyl from the occupational environment may occur via inhalation and dermal contact. Concentrations of biphenyl in the air of one facility producing biphenyl-impregnated paper were reported to range from 4.4 to 128 mg/m^3 in 1959 and from 0.6 to 123 mg/m^3 in 1970 (Haekkinen et al., 1973). In a nylon production facility in which workers were exposed to a eutectic mixture of 26.5% (w/w) biphenyl and 73.5% (w/w) biphenyl ether, time-weighted average concentrations of biphenyl were reported to range from 0.24 to 1.28 mg/m^3 (Dorgelo et al., 1985). Coke oven emissions to indoor air at a coking plant in Australia contained 0.2–0.5% biphenyl (Kirton et al., 1991). In a Polish bituminous pulp production facility, reported time-weighted average concentrations (1988–89) of biphenyl ranged from 0.5 to 0.6 ：g/m^3 (Baranski, 1991). In a study of two Canadian pilot-scale coal liquefaction facilities, the levels of biphenyl were below the detection limit of 60 ：g/m^3 (Leach et al., 1987).

7. COMPARATIVE KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

Studies providing quantitative information on the absorption or distribution of biphenyl in humans were not identified. In various species of experimental animals, the absorption of biphenyl following oral exposure has been inferred by the detection of metabolites in the urine and faeces. Biphenyl is oxidized by multifunctional oxygenases, irrespective of the route of exposure. Mono-, di-, and trihydroxy metabolites of biphenyl have been identified in the urine of exposed species. 4-Hydroxybiphenyl has been observed as the major metabolite in rats, rabbits, guinea-pigs, and pigs; minor metabolites include mono-, di-, and trihydroxymethoxy biphenyls, dihydrodiols, and hydroxydihydrodiols. The phenolic compounds are conjugated with sulfate or glucuronic acid. The formation of mercapturic acid as well as evidence of a metabolic pathway involving opening of the benzene ring have also been described (BUA, 1990). There is no evidence for enterohepatic circulation in different species (Meyer & Scheline, 1976; Meyer et al., 1976a; Meyer, 1977). On the basis of *in vitro* studies, the metabolism of biphenyl is not restricted to the liver (Bend et al., 1972; Hook et al., 1972; Matsubara et al., 1974; Prough & Burke, 1975; Hook & Bend, 1976; Powis et al., 1987). Based upon total cytochrome P-450 content, biphenyl-4-hydroxylase activity was higher in pulmonary microsomes than in liver microsomes (Hook et al., 1972; Hook & Bend, 1976). A time-dependent covalent binding of [^{14}C]biphenyl to mouse hepatic microsomal proteins has been observed after metabolic activation (Tanaka et al., 1993).

In rats, rabbits, and pigs, most biphenyl metabolites are excreted in the urine (BUA, 1990). Following an oral dose of 100 mg [^{14}C]biphenyl/kg body weight, rats excreted 82% of the administered radioactivity (76% in urine) within 24 h. The recovery rate after 4 days was 92%, with 7% of the administered radioactivity detected in the faeces and traces in the exhaled air. Eight days after administration, radioactivity in the tissues was 0.6% of the applied dose (Meyer et al., 1976b). In none of the species examined was unmetabolized biphenyl found in the urine (BUA, 1990).

8. EFFECTS ON LABORATORY MAMMALS AND *IN VITRO* TEST SYSTEMS

8.1 Single exposure

The acute oral toxicity of biphenyl is moderate. The LD_{50} for rats and mice is >1900 mg/kg body weight (BUA, 1990). Acute effects include polyuria, accelerated breathing, lacrimation, anorexia, weight loss, muscular weakness and coma, fatty liver cell degeneration, severe nephrotic lesions (often manifested as acute and subacute glomerulotubular nephritis), degenerative myocardial lesions, pulmonary hyperaemia, and, occasionally, alveolar oedema. Interstitial and lobular pneumonitis have been observed in animals that survived for a few days.

The LC_{50} (4-h) for the mouse is >43 ppm (275 mg/m^3). During exposure, hyperactivity and mild respiratory discomfort have been observed; however, these effects were not evident at the end of a 14-day recovery period. Gross pathological examination performed on surviving animals revealed slight lung congestion (Sun Co. Inc., 1977a). In an inhalation study conducted with Sprague-Dawley rats, no effects were

observed after a 6-h exposure to 0.8 or 3 ppm (5.1 or 19.2 mg/m^3) biphenyl at temperatures of approximately 26 °C or 32 °C, respectively (Monsanto Co., 1959). No treatment-related alterations in appearance, demeanour, food consumption, or survival were observed following a 7-h inhalation exposure of rats to 3 g biphenyl/m^3 (nominal concentration); no detailed information on the methods or particle size of the substance were presented (Dow Chemical Co., 1974).

Information on the acute toxicity of biphenyl associated with dermal exposure was not identified.

8.2 Irritation and sensitization

Biphenyl is non-irritating to both intact and scarified rabbit skin. The substance was slightly irritating when applied to rabbits' eyes in an eye irritation test (BUA, 1990).

In a guinea-pig maximization test conducted according to OECD Guideline 406, there was reportedly no evidence of a skin sensitizing potential for biphenyl (Dreist & Kolb, 1993).

8.3 Short-term exposure

8.3.1 Oral exposure

In the studies cited below, the histopathological examination was focused on the urinary system. In a study in which male and female Wistar rats were fed 0, 50, 150, 300, or 450 mg biphenyl/kg body weight per day via the diet for 21 days, increased relative kidney weights and polycystic renal changes (with increased urine volume and specific gravity) were observed at doses of 50 and 150 mg/kg body weight per day, respectively. An increase in urine volume, specific gravity, and absolute kidney weight as well as polycystic renal changes were also observed in rats administered 500 or 1000 mg biphenyl/kg body weight per day in the diet for 14 days (Søndergaard & Blom, 1979).

When male albino rats were administered diets containing 0, 1000, 2500, 5000, or 10 000 mg biphenyl/kg (estimated intakes of 0, 75, 188, 375, or 750 mg/kg body weight per day) for 26 days, there was a dose-dependent (at doses of $188 mg/kg body weight per day) intensification of cloudiness in the urine, associated with an increase in precipitate formation in samples, which had been cooled or treated with sulfosalicylic acid. The precipitate consisted of free 4-hydroxybiphenyl and its glucuronide. These effects were largely reversible during a 28-day recovery period (Booth et al., 1956, 1961).

8.3.2 Inhalation exposure

No evidence of histopathological changes in the lung, trachea, liver, kidney, or spleen were observed in male and female mice exposed by inhalation to 25 or 55 ppm (about 160 or 350 mg/m^3) biphenyl for 7 h/day, 5 days/week, for 2 weeks (Sun Co. Inc., 1977b).

8.3.3 Dermal exposure

In rabbits, the repeated dermal application (20 in total) of purified biphenyl (0.5 g/kg body weight) for 2 h/day, 5 days/week, produced decreased body weight; one animal died after 8 applications. A decrease in body weight was also observed after repeated dermal application of technical biphenyl. In both studies, no effect upon the skin was observed. Histopathological examination revealed minimal changes in the heart, liver, kidneys, and, in some cases, spleen (no further details provided) (Deichmann et al., 1947). No adverse effects were observed when biphenyl was applied (8 h/day, 5 days/week, for a total of 30 applications) to the intact and abraded skin of rabbits at doses of 600 or 2000 mg/kg body weight per day (no further information provided) (Newell, 1953).

8.4 Long-term exposure

8.4.1 Subchronic exposure

8.4.1.1 Oral exposure

In all of the studies cited below, the histopathological examination was focused on the urinary system. A summary of the effects related to this specific endpoint (changes in kidneys, ureter, and urinary bladder) for both subchronic and chronic exposures is provided in Table 1.

Effects on the urinary tract (i.e. an increased number of microcalculi in urinary sediment, simple hyperplasia of the bladder epithelium) were observed in male F344 rats administered 5000 mg biphenyl/kg (estimated intake 252 mg/kg body weight per day) in the diet for 8 weeks. Morphological changes and the increased synthesis of DNA detected in the bladder epithelium after 4 weeks were attributed to constant irritation by the microcalculi (Shibata et al., 1989a).

In male B6C3F$_1$ mice, no changes in the urinary pH or in levels of DNA synthesis in the urinary bladder were noted after administration of 0 or 10 000 mg biphenyl/kg in the diet (0 or 1500 mg/kg body weight per day) over a period of 8 weeks. The urinary Na^+ concentration was significantly lower in mice administered 1500 mg/kg body weight per day compared with controls only at week 4 (Tamano et al., 1993).

Table 1: Summary of the effects of repeated biphenyl administration via diet on urine status, urinary bladder, and kidneys.

Species/strain/ sex	Application/duration	NO(A)EL (mg/kg)	Urine status	Urinary bladder	Kidneys	Reference
rat/F344/male	0 or 5000 mg/kg 8 weeks	<5000	crystals with microcalculi in urinary sediment	simple hyperplasia and increased DNA synthesis in the urothelium	not examined	Shibata et al. (1989a)
rat/F344/male	0 or 5000 mg/kg up to 24 weeks	<5000	microcalculi	simple hyperplasia, papillary or nodular hyperplasia of the urothelium after $16 weeks	increase in absolute/relative kidney weights; no morphological changes of the renal papillae or pelvis; no changes in DNA synthesis in the renal papillae and pelvis; focal calcification of the renal medulla	Shibata et al. (1989b)
rat/albino/male and female	0, 1000, 2500, or 5000 mg/kg up to 24 weeks[a]	1000	$2500 mg/kg: increase in volume, turbidity, and precipitate after $30 days; urinary sediment: 4-hydroxy-biphenyl and its glucuronide; effects reversible	not examined	2500 mg/kg: morphological changes (tubular dilation) after $60 days 5000 mg/kg: morphological changes (tubular dilation) after $30 days; effects not completely reversible	Booth et al. (1961)
rat/F344/male	0 or 5000 mg/kg 32 weeks	<5000	increase in pH value and Na^+ concentration; urinary sediment: 4-hydroxybiphenyl	increased incidence of calculi; histopathology: no effects	not given	Kurata et al. (1986)
rat/Wistar/male	0, 1250, or 5000 mg/kg 36 weeks	1250	not given	5000 mg/kg: increased incidence of calculi in ureter and bladder	5000 mg/kg: increased incidence of calculi and increase in relative kidney weights	Shiraiwa et al. (1989)
rat/Wistar/male and female	0, 2500, or 5000 mg/kg 75 weeks	<2500	haematuria at $2500 mg/kg after $16 weeks	$2500 mg/kg: increased incidence of calculi (composed of magnesium ammonium phosphate) after $16 weeks in ureter (females) 5000 mg/kg: increased incidence of calculi in ureter and bladder after $16 weeks; bladder with calculi: simple or diffuse hyperplasia and papillomatosis of the urothelium	$2500 mg/kg: increased incidence of calculi (composed of protein) after $16 weeks; kidneys with stones: obstructive pyelonephritis, tubular atrophy, fibrosis 5000 mg/kg: increase in relative kidney weights in females	Takita (1983); Shiraiwa et al. (1989)
rat/Wistar/male and female	0, 630, or 1250 mg/kg 104 weeks	1250	not given	no urolithiasis (no further information given)	not given	Takita (1983)
rat/F344/DuCrj/ male and female	0, 500, 1500, or 4500 mg/kg 104 weeks	<500[b]	$500 mg/kg: decrease in protein (males) $1500 mg/kg: decrease in protein (females) 4500 mg/kg: increase in pH (males and females)	4500 mg/kg: increase in calculi and hyperplasia of the urothelium (males >> females); increased tumour incidence in males	$1500 mg/kg: increase in hyperplasia of the renal pelvis in females 4500 mg/kg: increase in calculi (males > females) and hyperplasia of the renal pelvis (males)	Japan Bioassay Research Center (1996)
mouse/B6C3F$_1$/ male	0 or 10 000 mg/kg 8 weeks	10 000	decreased Na^+ concentration at week 4	no changes in DNA synthesis of the urothelium	not given	Tamano et al. (1993)
mouse/B6C3F$_1$/ male	0 or 10 000 mg/kg 32 weeks	<10 000	small amounts of greyish white and finely granular material	simple hyperplasia and papillary or nodular dysplasia in 1/10 mice	interstitial nephritis in 5/10	Tamano et al. (1993)
mouse/Crj:BDF$_1$/ male and female	0, 667, 2000, or 6000 mg/kg 104 weeks	667	6000 mg/kg: decrease in protein and ketone body	no changes	$2000 mg/kg: mineralization of the medulla in females 6000 mg/kg: desquamation and mineralization of the pelvis in males	Japan Bioassay Research Center (1996)

[a] Plus a post-treatment observation period of 9 weeks.
[b] Effects were observed at the lowest dose tested.

In a range-finding study in which male and female Wistar rats were administered diets containing biphenyl at 0, 1250, 2500, 5000, 10 000, or 20 000 mg/kg (estimated intakes of 0, 94, 188, 375, 750, or 1500 mg/kg body weight per day) for 10 weeks, dose-dependent effects (i.e. reduction in weight gain; increased serum activities of aspartate transaminase, alanine transaminase, and lactate dehydrogenase; and an increase in blood urea nitrogen) were observed at all doses (Takita, 1983).

In male F344 rats (20 per group) administered 0 or 5000 mg biphenyl/kg in the diet (0 or 375 mg/kg body weight per day) for 24 weeks (5 rats per group were sacrificed after 4, 8, 16, or 24 weeks), reduced body weight gain and an increase in absolute/relative kidney weights without differences in feed intake were observed in the biphenyl-exposed rats. The analysis of the urine showed that administration of biphenyl was associated with the formation of microcalculi. The histopathological examination of the renal papillae or pelvis performed after 4, 8, 16, and 24 weeks revealed no morphological changes; the rate of DNA synthesis in the renal papillae and pelvis determined after 4 weeks of treatment was unchanged. In most of the treated animals, a focal calcification of the renal medulla (no further information given) was noted. The examination of the epithelium of the urinary bladder revealed a simple hyperplasia in 5/5 rats after 16 and 24 weeks and papillary or nodular hyperplasia in 3/5 rats at week 16 and in 5/5 rats at week 24; no data on controls were presented (Shibata et al., 1989b).

In albino rats (42 animals of each sex per group) given 0, 1000, 2500, or 5000 mg biphenyl/kg in the diet (0, 75, 188, or 375 mg/kg body weight per day) for up to 24 weeks, the urine analysis and histopathological investigations of the kidneys during the study (days 30, 60, and 120) showed no apparent effects at a dose level of 75 mg/kg body weight (Booth et al., 1961). In some animals, early indications of a kidney-damaging effect were observed at doses of 188 and 375 mg/kg body weight at 30 days — polyuria, increasing cloudiness of the urine, and initial morphological changes (tubular dilation) in the kidney. These effects increased in frequency and degree as the administrations progressed. The urinary sediment consisted of 4-hydroxybiphenyl and its glucuronide. During a subsequent 60-day observation period, the urinary status normalized; however, changes in kidneys were not completely reversible (a few dilated tubules and scars remained) (Booth et al., 1961).

In male F344 rats (25 per group) administered 0 or 5000 mg biphenyl/kg in the diet (0 or 375 mg/kg body weight per day) for 32 weeks, a reduction in body weight gain but no clinical signs of poisoning were observed in dosed animals. In urine, an increase in pH value and Na^+ concentration was noted. At terminal necropsy, calculi were found in the urinary bladder. The urinary sediment consisted mainly of 4-hydroxybiphenyl. No associated histopathology was detected upon microscopic examination of the urinary bladder (Kurata et al., 1986).

When groups (n = 25) of male Wistar rats were provided diets containing 0, 1250, or 5000 mg biphenyl/kg (0, 94, or 375 mg/kg body weight per day) for 36 weeks, a reduction in body weight, increased relative kidney weights, and an increase in the number of animals with stones in the kidneys (0/25, 0/25, and 4/25, respectively), ureter (0/25, 0/25, and 1/25, respectively), and urinary bladder (0/25, 0/25, and 3/25, respectively) were noted in the high-dose group (Shiraiwa et al., 1989).

8.4.1.2 Inhalation exposure

Exposure of groups (n = 50) of male and female CD-1 mice to 25 or 50 ppm (160 or 320 mg/m^3; analytical concentrations) biphenyl for 7 h/day, 5 days/week, for 13 weeks produced hyperaemia and focal haemorrhage in the lung and an increase in hyperplasia of the tracheal epithelium. As these effects were also observed in some unexposed controls, they were attributed to the method of aerosol generation (i.e. inhalation of hot air) (Sun Co. Inc., 1977c).

Marked species differences were observed in a study in which rabbits, rats, and mice were exposed by inhalation to biphenyl in the form of dust (50% biphenyl on zeolite) at 5, 40, or 300 mg/m^3, 7 h/day, 5 days/week, for up to 13 weeks. No adverse effects were observed in rabbits. Rats exposed to 40 or 300 mg biphenyl/m^3 exhibited increased mortality and irritation of the mucous membranes; no effects were observed following exposure to 5 mg/m^3. Mice were the most sensitive species. Exposure to 5 mg biphenyl/m^3 (the only concentration tested) resulted in slightly increased mortality, with all mice exhibiting irritation of the upper respiratory tract (no further information available). Necropsy of dead rats and mice revealed mainly inflammatory bronchopulmonary changes. No information on control animals or particle size was provided (Deichmann et al., 1947).

8.4.2 Chronic exposure and carcinogenicity

In older studies, which were not further taken into consideration because of the small number of animals used, limited documentation, and/or limited exposures, no increase in tumour incidence was observed in rats and mice when biphenyl was administered orally (at doses up to 750 mg/kg body weight per day for 2 years) (Ambrose et al., 1960; Innes et al., 1969) or following a single subcutaneous injection of 46.4 mg biphenyl/kg

body weight, in which the animals were examined macroscopically and microscopically after an 18-month observation period (NTIS, 1968).

In Wistar rats (50 animals of each sex per group) given 0, 2500, or 5000 mg biphenyl/kg in the diet (0, 188, or 375 mg/kg body weight per day) for 75 weeks, dose-dependent effects (i.e. reduction in weight gain; alterations in serum activities of aspartate transaminase [increased and decreased], alanine transaminase [increased], and lactate dehydrogenase [increased]; and an increase in blood urea nitrogen) and a dose-dependent increase in stones of the kidney (females: 0/43, 1/43, 18/39; males: 0/44, 6/46, 15/47) and ureter (females: 0/43, 1/43, 2/39; males: 0/44, 0/46, 2/47), accompanied by haematuria as early as 16 weeks after initiation of exposure, were seen at $188 mg/kg body weight. At 375 mg/kg body weight, the relative kidney weights were significantly increased in females, and an increase in stones of the urinary bladder was seen in males and females (females: 0/43, 0/43, 6/39; males: 0/44, 0/46, 13/47). The histopathological examination of the urinary bladder with stones revealed simple or diffuse hyperplasia and papillomatosis of the epithelium, but no cancerous changes. The overall tumour incidence was not increased compared with controls. Kidneys with stones exhibited obstructive pyelonephritis, tubular atrophy, and fibrosis. Kidney stones were composed of protein, whereas urinary stones were composed of magnesium ammonium phosphate (Takita, 1983; Shiraiwa et al., 1989).

No urolithiasis and no increased overall tumour incidence compared with controls were observed in Wistar rats (50 animals of each sex per group) provided with diets containing 0, 630, or 1250 mg biphenyl/kg (0, 47, or 94 mg/kg body weight per day) for 104 weeks. Dose-dependent effects (i.e. reduction in weight gain; alterations in serum activities of aspartate transaminase [decreased], alanine transaminase [increased and decreased], and lactate dehydrogenase [increased and decreased]) were noted at both doses; 47 mg/kg body weight is considered the lowest-observed-(adverse-) effect level, or LO(A)EL (Takita, 1983).

In a study with F344/DuCrj rats performed according to standard protocols and described in sufficient detail, a significant increase in neoplastic and non-neoplastic lesions of the urinary bladder and a significant increase in calculi within the urinary bladder were observed in high-dose males, after the animals had been given diets containing 0, 500, 1500, or 4500 mg biphenyl/kg (0, 38, 113, or 338 mg/kg body weight per day) for 104 weeks. In males and females, a dose-dependent increase in hyperplasia of the epithelium of the renal pelvis was seen. The results of the histopathological findings in the urinary bladder and kidneys are summarized in Table 2. Other findings included increased serum enzyme levels (alkaline phosphatase, aspartate transaminase, and alanine transaminase) and an increased urea nitrogen level in low-dose males and mid-dose females, which became more pronounced with increasing doses. In mid- and high-dose females and high-dose males, haematological effects (i.e. reduced haemoglobin concentration and haematocrit) were noted (Japan Bioassay Research Center, 1996). From this study, a LOEL of 38 mg/kg body weight was derived.

In a study in which groups of male and female Crj:BDF_1 mice were given diets containing 0, 667, 2000, or 6000 mg biphenyl/kg (0, 100, 300, or 900 mg/kg body weight per day) for 104 weeks, a slight increase in liver tumours (hepatocellular adenomas and carcinomas) and basophilic cell foci of the liver was observed in the females at doses of 300 and 900 mg/kg body weight per day; however, the effects were not concentration dependent (Japan Bioassay Research Center, 1996) (see Table 3). In the male and female mice, degenerative changes of the respiratory epithelium of the nasal cavity and nasopharynx were observed at doses of $100 mg/kg body weight per day or $300 mg/kg body weight per day, respectively. Other findings included variations in serum enzyme levels (increase in alkaline phosphatase, aspartate transaminase, and alanine transaminase) and an increased urea nitrogen level in the low-dose males and females, which became more pronounced with increasing doses. In female mice receiving $300 mg biphenyl/kg body weight per day and in the high-dose males, degenerative changes in the kidney (increased mineralization of the inner stripe of the outer medulla, increase in desquamation of the epithelium of the renal pelvis) were also observed. Body weight gain and food consumption were reduced in the high-dose animals (Japan Bioassay Research Center, 1996).

Information on the toxicological effects of biphenyl following chronic inhalation or dermal exposure were not identified.

8.4.2.1 Tumour promotion

A number of studies have investigated the tumour-promoting potential of biphenyl. Kurata et al. (1986) considered biphenyl a tumour promoter, based upon the results of a study in which groups of male F344 rats were administered drinking-water containing 0.05% *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine (BBN) (as an initiator) for 4 weeks, followed by 0.5% biphenyl in the diet (estimated intake of approximately 375 mg/kg body weight per day) for a further 32 weeks, after which time the animals were examined histopathologically. The results are provided in Table 4. The effects of biphenyl were attributed to the increased Na^+ content in the urine of exposed rats, as well as to crystals containing mainly 4-hydroxybiphenyl detected in the urine.

Table 2: Data from Japanese cancer bioassay with male and female rats fed biphenyl in the diet for 2 years.[a]

	Male rats				Female rats			
End-point	**0 mg/kg**	**500 mg/kg**	**1500 mg/kg**	**4500 mg/kg**	**0 mg/kg**	**500 mg/kg**	**1500 mg/kg**	**4500 mg/kg**
survival rate	37/50	41/50	38/50	31/50	44/50	38/50	44/50	37/50
urinary bladder: neoplastic lesions								
transitional cell papilloma	0	0	0	10/50	0	0	0	0
transitional cell carcinoma	0	0	0	24/50 (p = 0.0001)[b]	0	0	0	0
squamous cell papilloma	0	0	0	1/50	0	0	0	0
squamous cell carcinoma	0	0	0	1/50	0	0	0	0
urinary bladder: non-neoplastic lesions (transitional epithelium)								
simple hyperplasia	0	0	0	12/50	0	0	1/50	1/50
nodular hyperplasia	0	0	0	40/50	1/50	0	0	5/50
papillary hyperplasia	0	0	0	17/50	0	0	0	4/50
basal cell hyperplasia	0	0	0	27/50	0	0	0	4/50
squamous cell hyperplasia	0	0	0	13/50	0	0	0	1/50
squamous cell metaplasia	0	0	0	19/50	0	0	0	4/50
inflammatory polyps	0	0	0	10/50	0	0	0	0
calculi	0	0	0	43/50	0	0	0	8/50
kidney								
mineralization — papilla	9/50	9/50	14/50	23/50	2/50	6/50	3/50	13/50
mineralization — pelvis	9/50	6/50	10/50	18/50	12/50	12/50	18/50	27/50
calculi	0/50	0/50	0/50	13/50	0/50	0/50	0/50	3/50
desquamation — pelvis	1/50	0/50	0/50	11/50	0/50	0/50	0/50	2/50
simple hyperplasia of the transitional epithelium	6/50	8/50	5/50	19/50	3/50	5/50	12/50	25/50
nodular hyperplasia of the transitional epithelium	0/50	1/50	1/50	21/50	0/50	0/50	1/50	12/50
ureter dilatation	0/50	0/50	1/50	14/50	0/50	0/50	0/50	6/50

[a] From Japan Bioassay Research Center (1996); [b] Fisher Exact Test.

Table 3: Data from Japanese cancer bioassay with male and female mice fed biphenyl in the diet for 2 years.[a]

	Male mice				Female mice			
End-point	**0 mg/kg**	**667 mg/kg**	**2000 mg/kg**	**6000 mg/kg**	**0 mg/kg**	**667 mg/kg**	**2000 mg/kg**	**6000 mg/kg**
survival rate	35/50	41/50	41/50	39/50	31/50	22/50	25/50	32/49
liver: neoplastic lesions								
hepatocellular carcinoma	8/50	8/49	5/50	4/50	1/50	5/50 (p = 0.121)[b]	7/50 (p = 0.043)[b]	5/49 (p = 0.1163)[b]
hepatocellular adenoma	8/50	6/49	7/50	3/50	2/50	3/50 (p = 0.4909)[b]	12/50 (p = 0.016)[b]	10/49 (p = 0.0251)[b]
historical control data: carcinoma: 171/700 with a range of 1/50 – 19/50 adenoma: 119/700 with a range of 2/50 – 15/50					historical control data: carcinoma: 15/699 with a range of 0/50 – 2/50 adenoma: 33/699 with a range of 1/50 – 5/50			
basophilic cell foci	0/50	6/49	1/50	2/50	1/50	1/50	12/50	6/49

[a] From Japan Bioassay Research Center (1996).
[b] Fisher Exact Test.

Table 4: Results of the tumour-promoting potential (urinary bladder) of biphenyl in male rats.[a]

	Hyperplasia		Papilloma		Carcinoma	
	n	**(%)**	***n***	**(%)**	***n***	**(%)**
biphenyl only (21 rats)	0	0	0	0	0	0
BBN[b] only (24 rats)	6	!25	3	!12	0	0
BBN and biphenyl (18 rats)	17	!94	15	!83	11	!61

[a] Taken from Kurata et al. (1986).
[b] BBN = *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine.

Table 5: Results of the tumour-promoting potential (urinary bladder) of biphenyl in male mice.[a]

	Hyperplasia		Papillary or nodular dysplasia		Carcinoma	
	n	(%)	*n*	(%)	*n*	(%)
biphenyl only (10 mice)	1	!10	1	!10	0	0
BBN[b] only (20 mice)	12	!60	2	!10	0	0
BBN and biphenyl (20 mice)	14	!70	1	!5	0	0

[a] Taken from Tamano et al. (1993).
[b] BBN = *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine.

In a study in which male Wistar rats were administered 0.1% *N*-ethyl-*N*-hydroxyethylnitrosamine in the diet for 2 weeks, followed by 0, 0.125, or 0.5% biphenyl in the diet for 34 weeks, exposure to biphenyl had no effect upon the incidence of dysplastic foci and renal cell tumours induced by *N*-ethyl-*N*-hydroxyethylnitrosamine; however, an increase in stones of the kidneys, ureter, and bladder was observed in rats administered 0.5% biphenyl with or without *N*-ethyl-*N*-hydroxyethylnitrosamine (Shiraiwa et al., 1989).

Tamano et al. (1993) maintained male B6C3F$_1$ mice on drinking-water containing 0.05% BBN supplement for 4 weeks. After the BBN pre-treatment, the animals received diets with 10 000 mg biphenyl/kg (1500 mg/kg body weight per day) for 32 weeks. At the end of the study, the urinary bladder and kidneys were examined histopathologically. The results are provided in Table 5. In mice exposed to BBN and biphenyl, the average food consumption and the final body weight were reduced, whereas the relative weight of the urinary bladder was increased. The induction of simple hyperplasia and papillary or nodular dysplasia of the urinary bladder in 1/10 mice treated with biphenyl only was associated with urolithic residues (small amounts of greyish white and finely granular material). In mice treated with biphenyl with or without BBN pre-treatment, the incidence of interstitial nephritis in the kidneys was 65 and 50%, respectively.

In an early study in which albino mice “initiated” with a single dermal application of 9,10-dimethyl-1,2-benzanthracene (0.3% in benzene) received dermal applications of biphenyl (20% in benzene) twice weekly for 15 weeks, no skin papillomas or carcinomas were observed in either the vehicle controls or exposed mice 16 weeks after application of the initiator (Boutwell & Bosch, 1959).

8.5 Genotoxicity and related end-points

The results of the *in vitro* tests with biphenyl are summarized in Table 6. *In vitro* studies with bacteria have yielded no evidence of mutagenic potential for biphenyl, whereas gene mutation and mitotic recombination were observed with *Saccharomyces cerevisiae* D7 in the presence or absence of metabolic activation. However, no gene conversion was observed with *S. cerevisiae* D3. Testing in mammalian cells has produced positive results for gene mutations and clastogenicity in the presence of metabolic activation and negative results in the absence of metabolic activation.

In an *in vivo* rat cytogenetic assay of bone marrow cells, the incidence of chromosomal aberrations was not increased (no further information available) (Kawachi et al., 1980). The exposure by inhalation of male Sprague-Dawley rats to 64 or 320 mg biphenyl/m^3 (as dust aerosol) for 7 h/day, 5 days/week, for 30 days (20 exposures in total) reportedly did not increase the frequency of chromosomal aberrations in the bone marrow (Dow Chemical Co., 1976). However, owing to insufficient documentation (i.e. no data available concerning dust particle size distribution or cell harvesting times) and the low number of metaphase cells examined (i.e. 50 cells per animal), the validity of this study cannot be ascertained.

The results of *in vitro* studies indicate that biphenyl has mutagenic potential; in the absence of reassurance from reliable results from *in vivo* tests, it is assumed that exposure to biphenyl may be associated with a mutagenic risk.

8.6 Reproductive and developmental toxicity

Available data on the reproductive or developmental toxicity of biphenyl are limited. In Wistar rats administered (by gavage) 0, 125, 250, 500, or 1000 mg biphenyl/kg body weight (in corn oil) on days 6–15 of gestation, no maternal toxicity occurred at doses of #500 mg/kg body weight. In the highest dose group, 5 of 20 rats died. Also at 1000 mg/kg body weight, reduced fetal weight and an increased number of dead and resorbed fetuses were noted; however, these values were statistically not significantly different from those of control animals. At doses of $500 mg/kg body weight, there were non-significant increases in the incidence of fetuses with missing or non-ossified sternebrae (Khera et al., 1979).

Table 6: Results of *in vitro* genotoxicity studies on biphenyl.

Species (test system)	End-point	Concentration range	Results[a] Without MA	With MA	References
Salmonella typhimurium TA92, TA94, TA97, TA97a, TA98, TA100, TA102, TA1532, TA1535, TA1537, TA1538, TA2636	Reverse mutations	0–5000 :g/plate	!	!	Cline & McMahon (1977); Purchase et al. (1978); Kawachi et al. (1980); NTP (1980); Bronzetti et al. (1981); Probst et al. (1981); Waters et al. (1982); Haworth et al. (1983); Pagano et al. (1983, 1988); Ishidate et al. (1984); Fujita et al. (1985); Brams et al. (1987); Bos et al. (1988); Glatt et al. (1992)
Escherichia coli WP2, WP2 uvrA$^-$	Gene mutations	0.1–1000 :g/ml	!	!	Cline & McMahon (1977); Probst et al. (1981); Waters et al. (1982)
E. coli PQ37	DNA damage	2.4–154 :g/ml	!	!	Brams et al. (1987)
Bacillus subtilis rec assay	DNA damage	no data	!	0	Kawachi et al. (1980)
Saccharomyces cerevisiae D7	Gene mutation/ gene conversion	#154 :g/ml	+	+	Pagano et al. (1983)
S. cerevisiae D3	Gene conversion	no data	!	!	Waters et al. (1982); Zimmermann et al. (1984)
Chinese hamster cells (V79)	Gene mutation	0–100 :g/ml	!	+	Glatt et al. (1992)
L5178Y TK$^{+/-}$ cells (mouse lymphoma assay)	Gene mutation	0–61 :g/ml	!	(+)	Wangenheim & Bolcsfoldi (1988)
Chinese hamster cells (CHL)	Chromosomal aberration	0–125 :g/ml	!	0	Ishidate & Odashima (1977); Kawachi et al. (1980); Sofuni et al. (1985)
Chinese hamster cells (CHL)	Chromosomal aberration	0–20 :g/ml	!	+	Sofuni et al. (1985)
Chinese hamster cells (DON)	Chromosomal aberration	15.4–154 :g/ml	!	0	Abe & Sasaki (1977)
Rat hepatocytes	Unscheduled DNA synthesis	0.002–154 :g/ml	0	!	Williams (1978); Brouns et al. (1979); Probst et al. (1981)
Chinese hamster cells (CHL)	Sister chromatid exchange	no data	!	0	Kawachi et al. (1980)
Chinese hamster cells (DON)	Sister chromatid exchange	15.4–154 :g/ml	!	0	Abe & Sasaki (1977)
L5178Y cells (alkaline unwinding assay)	DNA damage	0–231 :g/ml	!	+	Garberg et al. (1988)
human lung fibroblasts (WI-38 cells)	Unscheduled DNA synthesis	no data	!	!	Waters et al. (1982)
human fibroblasts (“nick translation assay”)	DNA damage	15.4 :g/ml	!	0	Snyder & Matheson (1985)

[a] !, negative; +, positive; (+) weakly positive; 0, not tested; MA, metabolic activation.

Compared with unexposed controls, litter size (the only parameter examined) was not affected in a study in which small numbers of male and female rats were administered diets containing 0.1 or 0.5% biphenyl (estimated intakes of 75 and 375 mg/kg body weight per day) before mating and throughout gestation (Ambrose et al., 1960). In an unpublished three-generation study, dietary biphenyl concentrations of 100 or 1000 mg/kg (estimated intakes of approximately 7.5 or 75 mg biphenyl/kg body weight per day) had no effect on reproduction in rats; after intake of 10 000 mg/kg (estimated intake of 750 mg/kg body weight per day), decreased fertility, litter size, and growth rate were noted (no further information available) (Stanford Research Institute, undated). Histopathological changes within the male and female reproductive systems were not observed in rats or mice administered biphenyl at 500–4500 mg/kg in the diet for 2 years (Japan Bioassay Research Center, 1996).

8.7 Immunological and neurological effects

Data on immunological and neurological effects of biphenyl in laboratory animals were not identified.

9. EFFECTS ON HUMANS

Information on effects on human health resulting from exposure to biphenyl are limited to case reports; epidemiological studies were not identified. In one

report, a single application of 0.5 ml of a 4% biphenyl solution (no further details provided) to the skin of the lower arm of two test subjects caused no apparent irritation (Macintosh, 1945). Biphenyl did not cause skin irritation in a study in which a solution of 23% biphenyl in oil was applied to the forearm three times per week for 8 weeks (Selle, 1952). In one human volunteer orally given 35 mg biphenyl per week for 13 weeks, no adverse effects were reported (Farkas, 1939). Cases of headache, nausea, and inflammation of the respiratory tract have been reported in workers exposed to biphenyl vapours (and other substances) during paper production (Weil et al., 1965). Liver damage and effects upon the central and peripheral nervous systems were attributed to long-term exposure to high concentrations of biphenyl (see section 6.2) in a case-study of workers engaged in the production of biphenyl-impregnated paper (Haekkinen et al., 1973). Chronic persistent hepatitis in a woman who had worked for 25 years in a citrus packing plant in which biphenyl-impregnated paper was used was attributed to the absorption of biphenyl through the skin and digestive tract (Carella & Bettolo, 1994).

10. EFFECTS ON OTHER ORGANISMS IN THE LABORATORY AND FIELD

10.1 Aquatic environment

The acute toxicity of biphenyl in aquatic organisms has been investigated in microorganisms, plants, invertebrates, and vertebrates; however, in several studies cited in the main source document (BUA, 1990), information on whether results were based on nominal or effective concentrations was either lacking or not clearly stated. For biphenyl, nominal concentrations may not correspond to the effective concentrations, as the water solubility of biphenyl is low (4.45 mg/litre at 20 °C) (test results with higher nominal effect concentrations have not been reported here) and its volatility significant. In tests with open systems and longer test durations, results based on nominal concentrations may lead to an underestimation of toxic effects because of evaporation of the chemical; therefore, emphasis has been placed on studies with lowest reported effect levels in which loss of the test substance was minimized.

Several studies were conducted on the toxic effects of biphenyl on mixed microbial cultures as well as on single bacterial species. The most sensitive species was *Photobacterium phosphoreum*, with a 30-min EC_{50} of 1.9 mg/litre in a bioluminescence inhibition test (BUA, 1990). For *Colpidium campylum*, one of three different species of ciliata tested, the minimal active concentration of biphenyl for the inhibition of cell proliferation after a 43-h exposure was 5.6 mg/litre (nominal concentration; test substance predissolved in acetone) (Dive et al., 1980). In studies on the reduction of photosynthesis, 3-h EC_{50} values of 3.86 and 1.28 mg/litre were determined with the unicellular green algae *Chlorella vulgaris* and *Chlamydomonas angulosa*, respectively (BUA, 1990).

Forty-eight-hour LC_{50} values from acute toxicity tests with *Daphnia magna* were in the range of 1.1–4.7 mg/litre when experiments were conducted in more or less tightly closed test vessels. From a test in a closed system with continuous flow, a 48-h LC_{50} of 0.36 mg/litre and a NOEC of 0.04 mg/litre were reported. In a reproduction test with *Daphnia magna* in the same closed continuous-flow system, the NOEC after 21 days' incubation was 0.17 mg/litre (LC_{50} = 0.23 mg/litre) (Gersich et al., 1989). In studies on the inhibition of food intake by the marine mussel *Mytilus edulis* in a static system with loosely covered (not airtight) test vessels, a 40-min EC_{50} of 0.3 mg biphenyl/litre was reported (Donkin et al., 1991). From static tests on the toxicity of biphenyl on freshwater fish, 96-h LC_{50} values in the range of 1.5–4.7 mg/litre have been reported, with rainbow trout (*Oncorhynchus mykiss*) and fathead minnow (*Pimephales promelas*) the most sensitive species (BUA, 1990).

10.2 Terrestrial environment

Biphenyl has weak bactericidal and fungistatic properties. In studies with numerous mould fungus species, biphenyl (applied as vapour or imbedded in solid media) caused a reversible inhibition (50–100%) of cellular proliferation. Suppression of sporogenesis and, in *Penicillium digitatum* and *Diplodia natalensis*, the occurrence of biphenyl-resistant mutants were observed. Yeast species showed little or no inhibition of cell proliferation following exposure to biphenyl (BUA, 1990).

In a plant growth inhibition test conducted according to OECD Guideline 208, a nominal NOEC of 100 mg/kg dry soil was reported for sorghum (*Sorghum bicolor*) and soya bean (*Glycine max*); a NOEC of >1000 mg biphenyl/kg was reported for the sunflower (*Helianthus annuus*) (Windeatt et al., 1991). Biphenyl mixed into soil inhibited growth of lettuce (*Lactuca sativa*) seedlings with a 7-day EC_{50} of 54 mg/kg (nominal concentration). At the end of incubation, the concentration of test substance in the soil had decreased to <10% of the initial level (Hulzebos et al., 1993).

Data on toxic effects of biphenyl on terrestrial animals and ecosystems were not identified.

11. EFFECTS EVALUATION

11.1 Evaluation of health effects

11.1.1 Hazard identification and dose–response assessment

There are limited data on the effects of biphenyl exposure on humans. The assessment of potential health hazards has relied primarily on studies conducted in laboratory animals. The acute oral toxicity of biphenyl is moderate. The chemical is not irritating to the skin and is slightly irritating to the eyes, and there is no evidence of skin sensitizing potential.

Aside from differences in mortality among laboratory species exposed subchronically to biphenyl-containing dusts, the available data on effects associated with the inhalation of biphenyl are insufficient to form the basis of an assessment of potential health hazards associated with long-term airborne exposure to this chemical.

In toxicological studies in which rodents have been administered diets containing biphenyl for various periods of time, effects on the urinary system have often been reported. A marked increase in the incidence of morphological (i.e. formation of calculi) and/or histopathological (e.g. hyperplasia, desquamation) effects has been observed within the urinary tract of male rats administered diets containing more than 2500 mg biphenyl/kg for periods ranging from 32 to 104 weeks (Takita, 1983; Kurata et al., 1986; Shiraiwa et al., 1989; Japan Bioassay Research Center, 1996). An increase in the occurrence of calculi within the urinary bladder has also been observed in female rats, but at a lower incidence than in males (Takita, 1983; Shiraiwa et al., 1989; Japan Bioassay Research Center, 1996). Similarly, in a long-term dietary study (Japan Bioassay Research Center, 1996), increased squamous metaplasia within the urinary transitional epithelium was also observed in female rats; again, however, the incidence was lower than that observed in males. In male mice, only 1 of 10 animals given a diet containing 10 000 mg biphenyl/kg (1500 mg/kg body weight per day) for 32 weeks developed simple hyperplasia and papillary or nodular dysplasia of the urinary bladder (Tamano et al., 1993). Effects on blood chemistry and haematological parameters have also been observed in animals administered biphenyl orally; these effects occurred in male and female rats and mice at intakes lower than those associated with the development of effects in the urinary bladder of male rats administered biphenyl (Takita, 1983; Shiraiwa et al., 1989; Japan Bioassay Research Center, 1996). For non-neoplastic effects, the LOEL was 38 mg/kg body weight per day based upon the development of alterations in haematological parameters (i.e. decreased haemoglobin concentration and haematocrit) in rats fed diets containing 0, 500, 1500, or 4500 mg biphenyl/kg (reported intakes of 0, 38, 113, or 338 mg/kg body weight per day) for 2 years (Japan Bioassay Research Center, 1996).

Although limited, the available information indicates that biphenyl has no reproductive or developmental effects at doses lower than those associated with the development of adverse effects in the parental generation.

In one study, an increased incidence of benign and malignant tumours within the urinary bladder was observed in male F344/DuCrj rats administered diets containing high levels (i.e. not less than 4500 mg/kg) of biphenyl for 2 years. Tumour incidence was not increased in female rats or in male or female Crj:BDF_1 mice (Japan Bioassay Research Center, 1996). In female mice, there were slight increases in the incidences of benign and malignant liver tumours in animals receiving biphenyl in the diet; however, the results were not dose dependent over the entire range of concentrations tested. In other studies, biphenyl exhibited tumour-promoting activity with respect to the development of bladder neoplasms in male rats (Kurata et al., 1986) but not in male mice (Tamano et al., 1993).

The mechanism by which high doses of biphenyl induce bladder tumours specifically in male rats has not been fully elucidated. There have been suggestions that for some non-genotoxic chemicals, the formation of such tumours is linked to the regenerative hyperplasia of the urinary epithelium, caused by the abrasion and damage to the urothelium that are produced by calculi formed within the urinary tract only at very high levels of exposure (Cohen, 1995). Owing to anatomical and physiological differences, male rats are considered to be more susceptible than female rats, mice, and humans to the development of bladder tumours via such a mechanism; it has therefore been suggested that the sex- and species-specific development of bladder tumours in male rats receiving high doses of biphenyl might not be strictly relevant to humans exposed to lower levels. However, the incidence of histopathological effects and calculi formation within the urinary bladder also increased in female rats administered biphenyl for 2 years, in the absence of bladder tumours (Japan Bioassay Research Center, 1996). Moreover, data identifying a direct association between calculi formation, regenerative hyperplasia of the urothelium, and the development of bladder tumours within individual male animals are not available. Biphenyl has been reported to be mutagenic and clastogenic in some, but not all, *in vitro* assays and to bind covalently to macromolecules (i.e. proteins) following metabolic activation; the available data have been considered inadequate to assess its genotoxicity *in vivo*. These considerations, coupled with

the structural relationship of 4-hydroxybiphenyl, a major metabolite of biphenyl, to the potent human bladder carcinogen 4-aminobiphenyl and the lack of critical information related to the mechanism by which these bladder tumours arise in male rats, could suggest that the development of bladder tumours in the male rats may not have been entirely due to effects associated with the formation of calculi within the urinary bladder. This observation, as well as the slightly increased incidence of liver tumours in female mice, raises some concerns with respect to the potential carcinogenicity of biphenyl to humans.

11.1.2 Criteria for setting guidance values for biphenyl

A provisional tolerable daily intake (TDI), based upon the development of effects in the blood of rats administered diets containing biphenyl for 2 years (Japan Bioassay Research Center, 1996), can be derived as follows:

$$\text{TDI} = \frac{38 \text{ mg/kg body weight per day}}{1000}$$

$$= 38 \text{ :g/kg body weight per day}$$

where:

38 mg/kg body weight per day is the lowest LOEL for the development of alterations in blood chemistry in rats provided diets containing biphenyl for 2 years. This intake is lower than intakes associated with the development of haematological effects, calculi, and histopathological changes in the bladder and/or kidneys in rats and the development of haematological and histopathological effects in mice administered biphenyl in the diet for 2 years.

1000 is the uncertainty factor (×10 for interspecies variation; ×10 for intraspecies variation; ×10 for extrapolation from a LOEL to a NOEL).

However, based upon the currently available data, there is some uncertainty surrounding the health-protective nature of the value, owing to lack of critical information concerning the mechanism by which biphenyl induces bladder tumours in male rats, the slight increase in hepatocellular tumours in female mice, and the potential genotoxicity of this substance. Because of this uncertainty, the TDI is designated provisional.

Available data were inadequate to serve as a basis for the derivation of guidance values for biphenyl in air.

11.1.3 Sample risk characterization

For the general population, there is insufficient information available concerning the intake of biphenyl from the general environment; therefore, comparisons with the provisional TDI are provided merely as an example. From limited information on the content of biphenyl in citrus fruits, the estimated daily intake is #375 ng biphenyl/kg body weight from each individual fruit consumed, while the estimated daily intake from tap-water is #0.16 ng/kg body weight. Assuming that a person consumes one citrus fruit per day, the estimated intake of biphenyl from drinking-water and citrus fruit consumption is approximately two orders of magnitude lower than the provisional TDI based upon the development of effects in the blood.

From a study on workers exposed in a plant producing biphenyl-impregnated paper, it can be derived that exposure to high biphenyl concentrations up to 128 mg/m^3 pose a hazard. Neurotoxic effects and liver damage have been observed.

Additional information is required to better define any potential carcinogenic risks that might be associated with exposure to biphenyl.

11.2 Evaluation of environmental effects

The atmosphere is likely the main target compartment for biphenyl; however, the chemical has been detected in all environmental compartments as a result of its release from vehicle emissions, heating, smoking, and industrial activities. Water, soil, and biota appear to be affected mainly in the direct vicinity of industrial activities. The decline in the levels of biphenyl in surface waters may be due to restrictions on the production and use of PCBs. There are no data available on the release of biphenyl into environmental compartments from industrial use, from the application of biphenyl-contaminated sewage sludge to arable land, from volatilization during the storage of treated fruits, and from leaching from preserved citrus fruits and their packaging materials in domestic waste dumps. Only estimated values are available for the photooxidation of biphenyl in the atmosphere, which is probably the most important degradation process in this compartment.

Biomagnification of biphenyl in higher trophic levels of the aquatic or terrestrial food-chain, based upon the potential of biphenyl to bioaccumulate, is expected to be of minor importance. For the aquatic compartment, a significant elimination of biphenyl can be expected as a result of evaporation and degradation. Furthermore, rapid metabolism of biphenyl in laboratory animals and low acute toxicity after ingestion have been reported.

Data on effect concentrations for terrestrial organisms and exposure levels in air and soil are insufficient for risk characterization for terrestrial organisms. A sample risk characterization with respect to the aquatic environment can be performed (based upon data derived from Germany) by calculating the ratio between a (local or regional) PEC (based on measured or model concentrations) and a PNEC (EC, 1996).

The annual average concentration of biphenyl (#0.5 :g/litre) measured in the 1990s in the Rhine River and its tributaries was used as a $PEC_{measured}$. A $PEC_{local\ (water)}$, based upon data derived from the effluent of the wastewater treatment plant of a German producer, may be calculated as follows:

$$PEC_{local\ (water)} = \frac{C_{effluent}}{(1 + K_{p\ (susp)} \times C_{susp} \times 10^{-6}) \times D}$$

$$= <0.0064\ :g/litre$$

where:

$C_{effluent}$ is <5 :g/litre, the concentration of biphenyl in wastewater in 1990 (BUA, 1990);

$K_{p\ (susp)}$ = 423, the suspended matter/water adsorption coefficient, estimated from the mean soil sorption coefficient (K_{oc}) of 4230 ($K_{p\ (susp)} = K_{oc} \times 0.1$, where 0.1 is the fraction of organic carbon in suspended matter, $f_{oc(susp)}$);

C_{susp} = 15 mg/litre (default value; EC, 1996), the concentration of suspended matter in the river; and

D = 781, the dilution factor for river flow, calculated from sewage treatment plant and river flow data (EC, 1996).[1]

A PNEC for surface waters may be calculated by dividing the lowest valid LC_{50} or NOEC by an appropriate assessment factor (equal to a safety factor):

$$PNEC = \frac{170\ :g/litre}{10}$$

$$= 1.7\ :g/litre$$

where:

170 :g/litre is the lowest NOEC from a chronic study with *Daphnia magna*; and

10 is the assessment factor. For biphenyl, based upon data for four trophic levels, including one long-term NOEC, the recommended assessment factor would be 100 (EC, 1996). However, because of its significant volatility and degradation, and as effect concentrations from a wide selection of species covering different taxonomic groups are reported, an assessment factor of 10 is used.

Therefore, based upon the annual average concentrations of biphenyl measured in the Rhine River and in industrial wastewater effluent in Germany, the $PEC_{measured}$/PNEC and $PEC_{local\ (water)}$/PNEC ratios are #0.29 and <0.04, respectively. In some jurisdictions (EC, 1996), chemicals with a PEC/PNEC ratio of <1 may not require implementation of risk reduction measures beyond those already in place.

12. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

The Joint FAO/WHO Meeting on Pesticide Residues has allocated an acceptable daily intake of biphenyl of 0–0.125 mg/kg body weight (JMPR, 1967).

Information on international hazard classification and labelling is included in the International Chemical Safety Card reproduced in this document.

13. HUMAN HEALTH PROTECTION AND EMERGENCY ACTION

Human health hazards, together with preventative and protective measures and first aid recommendations, are presented in the International Chemical Safety Card (ICSC 0106) reproduced in this document.

13.1 Advice to physicians

Treatment is symptomatic and supportive following intoxication. The clinical picture is characterized by central and peripheral nerve damage and liver injury in human poisoning. There is some evidence to indicate that electroencephalographic abnormalities could persist up to 1 or 2 years after exposure.

13.2 Health surveillance advice

Objective change in electroencephalogram and electroneuromyogram could be an indication of biphenyl poisoning in exposed individuals. Monitoring of liver

[1] Personal communication from Verband d. Textilhilfsmittel-, Lederhilfsmittel-, Gerbstoff- und Waschrohstoff-Industrie e.V., Frankfurt/M., Germany, to Bayer AG, 1996.

function could also be integrated into a medical surveillance programme.

13.3 Spillage

In the event of spillage, measures should be undertaken to prevent biphenyl from reaching drains and watercourses, because of its toxicity to aquatic organisms.

14. CURRENT REGULATIONS, GUIDELINES, AND STANDARDS

Information on national regulations, guidelines, and standards can be found in the International Register of Potentially Toxic Chemicals (IRPTC), available from UNEP Chemicals (IRPTC), Geneva.

The reader should be aware that regulatory decisions about chemicals taken in a certain country can be fully understood only in the framework of the legislation of that country. The regulations and guidelines of all countries are subject to change and should always be verified with appropriate regulatory authorities before application.

BIPHENYL

0106
April 1994

CAS No: 92-52-4
RTECS No: DU8050000
UN No:
EC No: 601-042-00-8

Diphenyl
Phenylbenzene
Dibenzene
$C_{12}H_{10}$ / $C_6H_5C_6H_5$
Molecular mass: 154.2

TYPES OF HAZARD/ EXPOSURE	ACUTE HAZARDS/SYMPTOMS	PREVENTION	FIRST AID/FIRE FIGHTING
FIRE	Combustible.	NO open flames.	Water spray, powder, AFFF, foam, carbon dioxide.
EXPLOSION	Finely dispersed particles form explosive mixtures in air.	Prevent deposition of dust; closed system, dust explosion-proof electrical equipment and lighting. Prevent build-up of electrostatic charges (e.g., by grounding).	
EXPOSURE		**PREVENT DISPERSION OF DUST!**	
Inhalation	Cough. Nausea. Vomiting.	Avoid inhalation of fine dust and mist. Local exhaust or breathing protection.	Fresh air, rest. Refer for medical attention.
Skin		Protective gloves.	Remove contaminated clothes. Rinse and then wash skin with water and soap.
Eyes	Redness. Pain.	Safety goggles, or eye protection in combination with breathing protection if powder.	First rinse with plenty of water for several minutes (remove contact lenses if easily possible), then take to a doctor.
Ingestion	(further see Inhalation).	Do not eat, drink, or smoke during work. Wash hands before eating.	Rinse mouth. Refer for medical attention.

SPILLAGE DISPOSAL	PACKAGING & LABELLING	
Sweep spilled substance into sealable containers; if appropriate, moisten first to prevent dusting. Carefully collect remainder, then remove to safe place (extra personal protection: A/P2 filter respirator for organic vapour and harmful dust).	Xi Symbol R: 36/37/38 S: (2-)23	Do not transport with food and feedstuffs.

EMERGENCY RESPONSE	STORAGE
NFPA Code: H 2; F 1; R 0;	Separated from food and feedstuffs and oxidants.

IPCS
International Programme on Chemical Safety

Prepared in the context of cooperation between the International Programme on Chemical Safety and the European Commission
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SEE IMPORTANT INFORMATION ON THE BACK.

IMPORTANT DATA

Physical State; Appearance
WHITE CRYSTALS OR FLAKES, WITH CHARACTERISTIC ODOUR.

Physical Dangers
Dust explosion possible if in powder or granular form, mixed with air.

Chemical Dangers
Reacts with oxidants.

Occupational Exposure Limits
TLV: 0.2 ppm; 1.3 mg/m^3 (ACGIH 1993-1994).

Routes of Exposure
The substance can be absorbed into the body by inhalation and by ingestion.

Inhalation Risk
A harmful contamination of the air can be reached rather quickly on evaporation of this substance at 20°C.

Effects of Short-term Exposure
The substance irritates the eyes and the respiratory tract.

Effects of Long-term or Repeated Exposure
The substance may have effects on the liver and nervous system, resulting in impaired functions.

PHYSICAL PROPERTIES

Boiling point: 256°C
Melting point: 70°C
Relative density (water = 1): 1.04
Solubility in water: none
Vapour pressure, Pa at 71°C: 133
Relative vapour density (air = 1): 5.3
Relative density of the vapour/air-mixture at 20°C (air = 1): 1.0
Flash point: 113°C c.c
Auto-ignition temperature: 540°C
Explosive limits, vol% in air: 0.6 (at 111°C) - 5.8 (at 166°C)
Octanol/water partition coefficient as log Pow: 3.16/4.09

ENVIRONMENTAL DATA

This substance may be hazardous to the environment; special attention should be given to water. In the food chain important to humans, bioaccumulation takes place, specifically in plants. It is strongly advised not to let the chemical enter into the environment because it persists in the environment.

NOTES

Do NOT take working clothes home. Dowtherm A is a trade name.

ADDITIONAL INFORMATION

LEGAL NOTICE Neither the EC nor the IPCS nor any person acting on behalf of the EC or the IPCS is responsible for the use which might be made of this information

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APPENDIX 1 — SOURCE DOCUMENTS

BUA-Stoffbericht Biphenyl (1,1'-Biphenyl). **Beratergremium fuer Umweltrelevante Altstoffe (Report No. 50; July 1990). VCH VerlagsGmbH, Weinheim**

BUA-Stoffbericht 133 (Ergaenzungsberichte II). **Beratergremium fuer Umweltrelevante Altstoffe (1994). VCH VerlagsGmbH, Weinheim**

For the BUA review process, the company that is in charge of writing the report (usually the largest producer in Germany) prepares a draft report using literature from an extensive literature search as well as internal company studies. This draft is subject to a peer review during several readings of a working group consisting of representatives from government agencies, the scientific community, and industry.

The English translation of BUA Report No. 50 (BUA Report Biphenyl (1,1'-Biphenyl). GDCh-Advisory Committee on Existing Chemicals of Environmental Relevance (July 1990). VCH VerlagsGmbH, Weinheim) was released in 1992. The English translation of its Supplementary Report No. 133 is in preparation.

APPENDIX 2 — CICAD PEER REVIEW

The draft CICAD on biphenyl was sent for review to institutions and organizations identified by IPCS after contact with IPCS national Contact Points and Participating Institutions, as well as to identified experts. Comments were received from:

Bayer AG, Leverkusen, Germany

Department of Health, London, United Kingdom

Department of Public Health, Albert Szent-Gyorgyi University Medical School, Szeged, Hungary

Environmental Health Directorate, Health Canada, Ottawa, Canada

International Agency for Research on Cancer, Lyon, France

Ministry of Health and Welfare, International Affairs Division, Government of Japan, Tokyo, Japan

Monsanto Europe SA, Louvain-La-Neuve, Belgium

National Institute for Working Life, Solna, Sweden

National Institute of Occupational Health, Budapest, Hungary

United States Department of Health and Human Services (National Institute of Environmental Health Sciences)

United States Environmental Protection Agency (Office of Pollution Prevention and Toxics; Office of Drinking Water)

APPENDIX 3 — CICAD FINAL REVIEW BOARD (Brussels, Belgium)

Brussels, Belgium, 18–20 November 1996

Members

Dr A. Aitio, Institute of Occupational Health, Helsinki, Finland

Dr K. Bentley, Director, Environment Policy Section, Commonwealth Department of Human Services and Health, Canberra, Australia

Mr R. Cary, Toxicology and Existing Substances Regulation Unit, Health and Safety Executive, Merseyside, United Kingdom

Dr J. de Fouw, National Institute of Public Health and Environmental Protection, Bilthoven, The Netherlands

Dr C. DeRosa, Director, Division of Toxicology, Agency for Toxic Substances and Disease Registry, Atlanta, GA, USA

Dr S. Dobson, Institute of Terrestrial Ecology, Monks Wood, Abbots Ripton, Huntingdon, Cambridgeshire, United Kingdom

Dr W. Farland, Director, National Center for Environmental Assessment, Office of Research and Development, US Environmental Protection Agency, Washington, DC, USA *(Chairperson)*

Dr T.I. Fortoul, Depto. Biologia Celular y Tisular, National University of Mexico and Environmental Health Directorate of the Health Ministry, Mexico D.F., Mexico

Dr H. Gibb, National Center for Environmental Assessment, US Environmental Protection Agency, Washington, DC, USA

Dr R.F. Hertel, Federal Institute for Health Protection of Consumers & Veterinary Medicine, Berlin, Germany

Mr J.R. Hickman, Environmental Health Directorate, Health Canada, Ottawa, Ontario, Canada

Dr T. Lakhanisky, Head, Division of Toxicology, Institute of Hygiene and Epidemiology, Brussels, Belgium *(Vice-Chairperson)*

Dr I. Mangelsdorf, Documentation and Assessment of Chemicals, Fraunhofer Institute for Toxicology and Aerosol Research, Hanover, Germany

Ms M.E. Meek, Head, Priority Substances Section, Environmental Health Directorate, Health Canada, Ottawa, Ontario, Canada

Dr K. Paksy, National Institute of Occupational Health, Budapest, Hungary

Mr D. Renshaw, Department of Health, London, United Kingdom

Dr J. Sekizawa, Division of Chem-Bio Informatics, National Institute of Health Sciences, Tokyo, Japan

Dr H. Sterzl-Eckert, GSF-Forschungszentrum für Umwelt und Gesundheit GmbH, Institut für Toxikologie, Oberschleissheim, Germany

Professor S. Tarkowski, Department of Environmental Health Hazards, The Nofer Institute of Occupational Medicine, Lodz, Poland

Dr M. Wallen, National Chemicals Inspectorate (KEMI), Solna, Sweden

Observers

Professor F.M.C. Carpanini,[1] Director, Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), Brussels, Belgium

Mr R. Haigh,[1] Head of Unit, Health and Safety Directorate, European Commission, Luxembourg

Mr B.U. Hildebrandt, Federal Ministry for the Environment, Nature Conservation and Nuclear Safety, Bonn, Germany

Mr P. Hurst,[1] Chemical and Consumer Policy Officer, Conservation Policy Division, World Wide Fund for Nature, Gland, Switzerland

Dr A. Lombard (CEFIC representative), ELF-ATOCHEM, Paris, France

Dr P. McCutcheon,[1] Environment, Consumer Protection and Nuclear Safety, European Commission, Brussels, Belgium

Dr R. Montaigne, Counsellor, Technical Affairs Department, European Chemical Industry Council (CEFIC), Brussels, Belgium

Dr M. Pemberton, ICI Acrylics, Lancashire, United Kingdom

Dr A. Smith, Environment Division, Organisation for Economic Co-operation and Development, Paris, France

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Dr M. Baril, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

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APPENDIX 4 — SPECIALIZED CICAD PEER REVIEW

Individuals contributing written comments to the specialized review of this CICAD were:

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Dr D. Singh, National Center for Environmental Assessment, US Environmental Protection Agency, Washington, DC, USA

Individuals participating in the review of the human health assessment (section 11.1) were:

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APPENDIX 5 — CICAD FINAL REVIEW BOARD (Washington, DC)

Washington, DC (USA), 8–11 December 1998

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RÉSUMÉ D'ORIENTATION

Ce CICAD relatif au biphényle a été préparé par l'Institut Fraunhofer de Toxicologie et de Recherche sur les Aérosols de Hanovre (Allemagne), principalement sur la base d'une étude préparée par le Comité consultatif allemand sur les substances chimiques importantes pour l'environnement (BUA, 1990) et d'un rapport complémentaire (BUA, 1994) afin d'évaluer les effets potentiels du biphényle sur l'Homme et l'environnement. On trouvera à l'appendice 1 des indications sur les sources documentaires utilisées ainsi que sur leur mode de dépouillement. Une étude bibliographique approfondie a été menée sur plusieurs bases de données jusqu'en juin 1996 à la recherche de données supplémentaires. Ce CICAD contient également les renseignements complémentaires recueillis par les points de contact et le Comité d'évaluation finale (Bruxelles, Belgique) lors du dépouillement des documents. Les renseignements concernant l'examen du CICAD par les pairs font l'objet de l'appendice 2. Ce CICAD a été approuvé en tant qu'évaluation internationale lors d'une réunion du Comité d'évaluation finale qui s'est tenue à Bruxelles (Belgique) du 18 au 20 novembre 1996. La liste des participants à cette réunion figure à l'appendice 3. Après avoir été révisé pour y incorporer les résultats d'une étude de cancérogénicité de 2 ans récemment achevée, le document a été soumis à des pairs pour deux séries d'évaluations écrites. En outre, la partie du document spécialement consacrée à l'évaluation des effets sur la santé humaine (à savoir la section 11.1), a été examinée lors d'une réunion qui s'est tenue le 7 décembre 1998 à Washington (Etats-Unis), dans les locaux du National Center for Environmental Assessment, US Environmental Protection Agency. La liste des personnes qui ont participé aux évaluations spécialisées du présent CICAD figure à l'appendice 4. Ce CICAD a été approuvé en tant qu'évaluation internationale lors de la réunion du Comité d'évaluation finale qui a eu lieu à Washington du 8 au 11 décembre 1998. La liste des participants à cette réunion figure à l'appendice 5. La fiche d'information internationale sur la sécurité chimique (ICSC 0106) établie par le Programme international sur la sécurité chimique (IPCS, 1993) est également reproduite dans ce document.

Le biphényle (CAS N° 92-52-4) est un hydrocarbure aromatique qui se présente à la température ambiante sous la forme d'un solide cristallin incolore. Il est utilisé comme intermédiaire dans la production de divers composés (par exemple, émulsifiants, azurants optiques, produits pour la protection des cultures, matières plastiques), comme fluide caloporteur, comme support de colorants pour textiles et papier à photocopie, comme solvant dans l'industrie pharmaceutique ou encore pour la conservation des agrumes.

Le biphényle existe à l'état naturel dans le goudron de houille, le pétrole brut et le gaz naturel. Parmi les sources artificielles de pollution par le biphényle figurent les unités qui produisent ou utilisent ce composé, les installations où l'on traite des agrumes ou des bois ou encore les décharges municipales. Il se forme lors de la combustion incomplète des huiles minérales et de la houille et on en trouve dans les gaz d'échappement des véhicules à moteur et dans l'air libéré dans l'atmosphère par les appareils de chauffage des installations industrielles ou des immeubles résidentiels. Des valeurs de 1 à 100 ng/m^3 sont caractéristiques de la concentration dans l'air ambiant. A l'intérieur des bâtiments, elles sont plus élevées (100-1000 ng/m^3), probablement par suite de la présence de fumée de cigarette, d'émissions provenant des appareils de chauffage et de garages situés dans le voisinage. Des mesures effectuées dans les années 70 ont donné des valeurs généralement inférieures à 5 ng/litre pour l'eau du robinet. On n'a pas connaissance de valeurs plus récentes. Dans les eaux superficielles, la concentration usuelle est inférieure à 500 ng/litre. Dans les sédiments, le sol et les êtres vivants, on n'a procédé à des dosages de biphényle qu'à proximité immédiate d'installations industrielles et de décharges.

Peu soluble dans l'eau, le biphényle s'évapore de ses solutions aqueuses. Sa principale voie de décomposition troposphérique est due à l'action des radicaux hydroxyles et la demi-vie calculée dans ces conditions est de l'ordre de 2 jours en moyenne. Le biphényle ne devrait pas s'hydrolyser dans les conditions qui règnent dans l'environnement. Il est biodégradable en aérobiose. D'après les données disponibles, il devrait être quasiment immobile dans le sol; sa probabilité d'infiltration dans les eaux souterraines est faible. Dans la chaîne alimentaire qui joue un rôle important pour l'alimentation humaine, il peut y avoir accumulation du biphényle, notamment dans les plantes. Toutefois, compte tenu de son potentiel de bioaccumulation, il ne semble pas qu'il puisse subir une bioamplification importante aux niveaux trophiques supérieurs de la chaîne alimentaire aquatique ou terrestre.

Le biphényle est bien absorbé dans les voies digestives et probablement aussi par la voie pulmonaire et percutanée. Chez les espèces étudiées, les métabolites du biphényle, principalement le 4-hydroxybiphényle, sont rapidement excrétés et presque exclusivement par la voie urinaire. Le biphényle est modérément toxique par voie buccale. Il n'est pas irritant pour la peau et n'irrite que très légèrement la muqueuse oculaire. Rien n'indique qu'il puisse provoquer une sensibilisation cutanée. Les études toxicologiques au cours desquels on a soumis les animaux de laboratoire à des expositions répétées au biphényle, ne permettent pas d'établir la valeur de la dose sans effet observable (NOEL) avec un

bon niveau de confiance. Une exposition subchronique par la voie respiratoire a provoqué l'apparition d'anomalies bronchopulmonaires, mais la littérature ne mentionne pas d'études toxicologiques de longue durée comportant une exposition par cette voie.

Les études toxicologiques comportant l'administration, pendant diverses périodes, de nourriture additionnée de biphényle à des rongeurs, font souvent mention d'effets aux niveau des voies urinaires. Chez des rats mâles ayant reçu une alimentation contenant plus de 2500 mg de biphényle par kg, on a observé une augmentation sensible dans l'incidence des effets morphologiques (par ex. formation de calculs) et histopathologiques (par ex. hyperplasie, desquamation) au niveau des voies urinaires. On a également observé une augmentation des calculs et des cas de métaplasie spinocellulaire vésicale chez des rattes, mais dans une proportion moindre que chez les mâles. Chez des souris mâles soumises pendant 32 semaines à un régime alimentaire comportant 10 000 mg de biphényle par kg (1500 mg par kg de poids corporel), on a observé une simple hyperplasie et une dysplasie papillomateuse ou nodulaire de la vessie, mais chez seulement un animal sur dix. Sur des animaux à qui on avait fait ingérer du biphényle, on a également observé des effets hématologiques (biochimiques et autres); ces effets peuvent être constatés chez des rats ou des souris mâles et femelles à des doses inférieures à celles qui produisent des effets sur la vessie des rats mâles. En ce qui concerne les effets non néoplasiques, la dose la plus faible produisant un effet observable (LOEL) se situait à 38 mg/kg p.c. par jour, le critère retenu étant l'apparition d'anomalies hématologiques (diminution du taux d'hémoglobine et de l'hématocrite) chez des rats ayant reçu pendant 2 ans une nourriture contenant respectivement 0, 500, 1500 ou 4500 mg/kg de biphényle (les doses indiquées étant égales à 0, 38, 113 ou 338 mg/kg p.c.).

Les études *in vitro* sur des bactéries n'ont pas mis en évidence d'activité mutagène. On a observé des mutations et des recombinaisons mitotiques chez *Saccharomyces cerevisiae* D7 avec ou sans activation métabolique. Les tests de génotoxicité sur cellules mammaliennes ont toutefois donné des résultats positifs en présence d'activation métabolique et des résultats négatifs en l'absence d'une telle activation. Une étude *in vivo* insuffisamment documentée et dont l'exécution laisse à désirer, n'a pas permis de constater la présence d'aberrations chromosomiques dans la moelle osseuse de rats exposés à du biphényle par la voie respiratoire. Les résultats d'autres études *in vitro* indiquent que le biphényle possède un pouvoir mutagène; dans ces conditions et devant le manque de fiabilité des résultats fournis par les études *in vivo*, on estime que le biphényle comporte un risque mutagène.

Chez des souris femelles, on a constaté une légère augmentation de l'incidence des tumeurs bénignes ou malignes du foie lorsque les animaux avaient reçu pendant 2 ans du biphényle mêlé à leur nourriture. Une augmentation de l'incidence des tumeurs vésicales a été observée chez des rats mâles, mais ni chez les femelles ni chez des souris des deux sexes, après administration d'une nourriture contenant une grande quantité de biphényle. On a avancé que ces tumeurs pouvaient être dues à l'hyperplasie régénérative de l'épithélium vésical provoquée par l'abrasion et les lésions que produisent les calculs, lesquels ne se forment que si l'exposition au biphényle est suffisamment intense. On pense également qu'en raison de différences anatomiques et physiologiques, ces tumeurs vésicales observées à forte doses chez des rats mâles et qui présentent une spécificité de sexe et d'espèce, n'ont guère de signification pour des sujets humains exposés à des doses plus faibles. Quoi qu'il en soit, 1) l'observation d'un accroissement de l'incidence des effets histopathologiques et la formation de calculs au niveau de la vessie, en l'absence de tumeurs vésicales , chez des rattes ayant reçu du biphényle pendant 2 ans, 2) l'absence de données permettant de mettre en évidence une association directe entre cette lithiase vésicale, l'hyperplasie régénérative de l'urothélium et l'apparition de tumeurs vésicales chez les rats mâles et 3) la génotoxicité potentielle du biphényle, incitent à penser que la formation de tumeurs vésicales chez les rats mâles n'est peut-être pas entièrement due à l'action des calculs. Cette observation, de même que les signes d'hépatotoxicité relevés chez les souris femelles, font craindre que le biphényle ne comporte un risque de cancérogénicité.

Les données relatives à la toxicité génésique du biphényle sont limitées. A part une étude portant sur trois générations de rats, qui a mis en évidence des effets indésirables (réduction de la fécondité, de la taille des portées et du taux de croissance), rien ne prouve que le biphényle puisse avoir des effets sur la reproduction ou le développement.

L'exposition, sur les lieux de travail, à des vapeurs ou à des poussières à forte teneur en biphényle entraîne une irritation des yeux et une inflammation des voies respiratoires. Une exposition pendant plusieurs années à de fortes concentrations de biphényle (jusqu'à 128 mg/m^3) a provoqué des lésions hépatiques et les anomalies neuronales permanentes; il est possible que dans ce cas, l'effet du contact cutané avec le composé se soit ajouté à celui de son absorption par la voie respiratoire.

On ne possède qu'un nombre limité de données sur la concentration du biphényle dans l'environnement et les renseignements qu'on peut en tirer sont insuffisants pour permettre une estimation raisonnable de la dose de composé absorbée. Il peut y avoir exposition par inhala-

tion (inhalation d'air pollué et utilisation de créosote contenant du biphényle pour la préservation du bois) ou par ingestion (lorsque le biphényle est utilisé comme conservateur d'agrumes).

Le biphényle est faiblement bactéricide et fongistatique. Lors d'études toxicologiques sur des organismes aquatiques représentant quatre niveaux trophiques, la concentration la plus faible sans effet observable (NOEC) pour l'espèce la plus sensible (*Daphnia magna*) a été trouvée égale 0,17 mg/litre lors de tests de longue durée. Le calcul donne une concentration sans effet prévisible (PNEC) de 1,7 ：g/litre en utilisant un facteur d'évaluation de 10, compte tenu des caractéristiques écotoxicologiques et du devenir environnemental du composé. On ne dispose pas, au sujet des effets toxiques du biphényle sur les organismes terrestres et les écosystèmes, de données valables permettant une évaluation du risque.

En raison de l'absence de données émanant d'autres régions du monde, l'évaluation du risque qui a été effectuée concerne spécifiquement l'Allemagne. A partir des concentrations mesurées dans les cours d'eau allemands au cours des années 90, on a obtenu un rapport de la concentration environnementale prévue (PEC) à la concentration sans effet prévisible (PNEC) qui est égal à #0,29. Un rapport PEC/PNEC <1 signifie qu'il n'y a vraisemblablement pas de risque important pour l'environnement.

RESUMEN DE ORIENTACIÓN

El presente CICAD, preparado por el Instituto Fraunhofer de Toxicología y de Investigación sobre los Aerosoles de Hannover, Alemania, se basa fundamentalmente en un examen preparado por el Comité Consultivo Alemán sobre las Sustancias Químicas Importantes para el Medio Ambiente (BUA, 1990), así como en un informe complementario (BUA, 1994) para evaluar los efectos potenciales del bifenilo en el ser humano y en el medio ambiente. En el apéndice 1 figuran los documentos originales y una descripción de sus procesos de examen. Se realizó asimismo una búsqueda bibliografía amplia en varias bases de datos en línea en junio de 1996 para identificar datos adicionales. También se ha incorporado a este CICAD nueva información adicional obtenida durante el examen efectuado por los servicios de información y por la Junta de Evaluación Final (Bruselas, Bélgica). En el apéndice 2 se presenta información relativa al examen colegiado de este CICAD. La Junta de Evaluación Final lo aprobó provisionalmente como evaluación internacional en una reunión celebrada en Bruselas (Bélgica) los días 18-20 de noviembre de 1996. En el apéndice 3 figura la lista de participantes en dicha reunión. Tras la incorporación de los datos relativos a la carcinogenicidad de esta sustancia obtenidos de una biovaloración de la carcinogenicidad de dos años de duración completada recientemente, el documento revisado se sometió a dos rondas de examen colegiado por escrito. Además, la parte del documento en la que se aborda específicamente la evaluación de la salud humana (es decir, la sección 11.1) se examinó en una reunión celebrada en el Centro Nacional para la Evaluación del Medio Ambiente, Organismo para la Protección del Medio Ambiente de los Estados Unidos, en Washington, DC (Estados Unidos) el 7 de diciembre de 1998. El apéndice 4 contiene la lista de quienes contribuyeron a los exámenes especializados adicionales del presente CICAD. Este CICAD se aprobó como evaluación internacional en una reunión de la Junta de Evaluación Final celebrada en Washington, DC (Estados Unidos), los días 8-11 de diciembre de 1998. En el apéndice 5 figura la lista de participantes en esta reunión. La Ficha internacional de seguridad química (ICSC 0106), preparada por el Programa Internacional de Seguridad de las Sustancias Químicas (IPCS, 1993), también se reproduce en el presente documento.

El bifenilo (CAS Nº 92-52-4), un hidrocarburo aromático, es una sustancia sólida incolora a temperatura ambiente. Se utiliza como intermediario en la producción de diversos compuestos (por ejemplo, emulsionantes, abrillantadores ópticos, productos para la protección de los cultivos, plásticos), como medio de transferencia de calor en fluidos térmicos, como colorante de textiles y papel para copias, como disolvente en la producción farmacéutica y en la conservación de cítricos.

El bifenilo se encuentra en la naturaleza en el alquitrán mineral, el petróleo bruto y el gas natural. Las fuentes antropogénicas de exposición en el medio ambiente incluyen las plantas de producción y elaboración, las instalaciones de conservación de cítricos o de madera y los vertederos municipales. Se forma bifenilo durante la combustión incompleta del aceite mineral y el carbón y está presente en los gases de escape de los vehículos y de las calderas de calefacción de las viviendas y las industrias. En la atmósfera, las concentraciones habituales de bifenilo oscilan entre 1 y 100 ng/m^3; en el aire de espacios cerrados los niveles son superiores (100-1000 ng/m^3), probablemente debido al humo de los cigarrillos y a las emisiones de las calderas de calefacción o de garajes cercanos. En las mediciones realizadas en los años setenta, las concentraciones de bifenilo en el agua de grifo eran normalmente inferiores a 5 ng/litro. No se conocen datos más recientes. En el agua superficial, las concentraciones suelen ser inferiores a 500 ng/litro. En los sedimentos, el suelo y la biota, sólo se midió el bifenilo en las cercanías de instalaciones industriales y vertederos.

El bifenilo se volatiliza de la solución acuosa y tiene una solubilidad baja en agua. La principal vía de degradación en la troposfera es la reacción con radicales hidroxilo, para la que se ha calculado una semivida de unos dos días. No cabe prever que la sustancia se hidrolice en las condiciones del medio ambiente. Es biodegradable en condiciones aerobias. Según los datos disponibles, el bifenilo debería mantenerse casi inmóvil en el suelo; la probabilidad de infiltración hacia el agua freática es baja. En la cadena alimentaria importante para el ser humano se puede producir bioacumulación, especialmente en las plantas; sin embargo, teniendo en cuenta la posible bioacumulación del bifenilo, cabe prever que su bioamplificación en los niveles tróficos superiores de la cadena alimentaria acuática o terrestre será de escasa importancia.

El bifenilo se absorbe bien a través del tracto gastrointestinal y posiblemente también por vía pulmonar y cutánea. En las especies examinadas, los metabolitos del bifenilo, sobre todo el 4-hidroxibifenilo, se excretan con rapidez y casi exclusivamente en la orina. La toxicidad aguda del bifenilo por vía oral es moderada. No es irritante de la piel y sólo ligeramente de los ojos. No hay pruebas de sensibilización cutánea. Los estudios de toxicidad con bifenilo tras la exposición repetida por inhalación no son adecuados para establecer con confianza una concentración sin efectos observados (NOEL). La exposición subcrónica por inhalación produjo cambios broncopulmonares, pero no se han encontrado en la bibliografía estudios de toxicidad prolongados tras la exposición por inhalación.

En estudios toxicológicos realizados con roedores que recibieron alimentos con bifenilo durante diversos

períodos de tiempo, se han notificado con frecuencia efectos en el sistema urinario. Se ha observado un aumento acentuado en la incidencia de efectos morfológicos (es decir, formación de cálculos) e histopatológicos (por ejemplo, hiperplasia, descamación) en el tracto urinario de ratas macho a las que se suministraron alimentos con concentraciones de bifenilo superiores a 2500 mg/kg. Se observó asimismo un aumento en la aparición de cálculos y metaplasia escamosa en la vejiga urinaria de ratas hembras, pero con una incidencia inferior a la registrada en los machos. En ratones macho, sólo uno de 10 animales que recibieron alimentos con 10 000 mg de bifenilo/kg (1500 mg/kg de peso corporal al día) durante 32 semanas presentó hiperplasia simple y displasia papilar o nodular en la vejiga urinaria. En animales que recibieron bifenilo por vía oral se detectaron asimismo efectos en la química sanguínea y los parámetros hematológicos; estos efectos se producen en ratas y ratones machos y hembras con ingestas inferiores a las asociadas con la aparición de efectos en la vejiga urinaria de las ratas machos tratadas con bifenilo. Para los efectos no neoplásicos, la concentración más baja de efectos observados (LOEL) fue de 38 mg/kg de peso corporal al día, basada en la aparición de alteraciones en los parámetros hematológicos (es decir, disminución de la concentración de hemoglobina y del valor hematócrito) en ratas a las que se suministraron alimentos que contenían 0, 500, 1500 ó 4500 mg de bifenilo/kg (ingestas notificadas de 0, 38, 113 ó 338 mg/kg de peso corporal al día) durante dos años.

En estudios *in vitro* con bacterias no se han obtenido pruebas de potencial mutagénico del bifenilo; con *Saccharomyces cerevisiae* D7, se observaron mutaciones genéticas y recombinación mitótica con activación metabólica y sin ella. Sin embargo, en pruebas de toxicología genética en células de mamíferos se obtuvieron resultados positivos con activación metabólica y negativos en su ausencia. En un estudio *in vivo* insuficientemente documentado y realizado de manera inadecuada, el bifenilo no indujo aberraciones cromosómicas en la médula ósea de ratas tras la exposición por inhalación. Los resultados de los estudios *in vitro* ponen de manifiesto que el bifenilo tiene potencial mutagénico; sin la garantía de resultados fidedignos de pruebas *in vivo*, se supone que la exposición al bifenillo se puede asociar con un riesgo mutagénico.

En ratones hembra, se produjo un ligero aumento de la incidencia de tumores hepáticos benignos y malignos en animales que recibieron bifenilo con los alimentos durante dos años. Se observó un aumento de la incidencia de tumores de vejiga en ratas machos, pero no en las ratas hembras o los ratones machos y hembras, que recibieron alimentos con concentraciones elevadas de bifenilo. Se ha indicado que la formación de dichos tumores de vejiga podría estar vinculada a la hiperplasia regenerativa del epitelio urinario, debida a la abrasión y las lesiones del urotelio producidas por los cálculos formados en el tracto urinario sólo con niveles muy altos de exposición; se ha señalado asimismo que, debido a las diferencias anatómicas y fisiológicas, la aparición de tumores de vejiga específicos del sexo y la especie en ratas macho que recibieron dosis elevadas de bifenilo tal vez no sea pertinente para las personas expuestas a niveles más bajos. Sin embargo, 1) las observaciones de una mayor incidencia de efectos histopatológicos y la formación de cálculos en la vejiga urinaria, en ausencia de tumores de vejiga, en ratas hembras tratadas con bifenilo durante dos años, 2) la falta de datos que establezcan una asociación directa entre la formación de cálculos, la hiperplasia regenerativa del urotelio y la aparición de tumores de vejiga en determinados animales machos, y 3) la genotoxicidad del bifenilo, podrían indicar que la aparición de tumores de vejiga en ratas macho tal vez no se deba completamente a los efectos asociados a la formación de cálculos en la vejiga urinaria. Esta observación, así como la prueba de hepatocarcinogenicidad en ratones hembras, despierta alguna preocupación con respecto a la carcinogenicidad potencial del bifenilo.

Los datos disponibles sobre la toxicidad reproductiva del bifenilo son limitados. Si se exceptúan los resultados obtenidos en un estudio de tres generaciones en ratas, en el que se observaron efectos adversos (disminución de la fecundidad, del tamaño de la camada y de la tasa de crecimiento), no se encontraron pruebas de que el bifenilo indujera efectos reproductivos o en el desarrollo.

La exposición a concentraciones elevadas de vapores o polvo de bifenilo en el lugar de trabajo produce irritación de los ojos e inflamación del tracto respiratorio. La exposición prolongada durante varios años a concentraciones elevadas de bifenilo (hasta 128 mg/m^3) provocó lesiones hepáticas y cambios neuronales persistentes; el contacto directo con la piel puede haber influido, además de la absorción a través del tracto respiratorio.

Los datos disponibles sobre las concentraciones de bifenilo en el medio ambiente general son limitados y la información es insuficiente para permitir una estimación razonable de su ingesta. La inhalación (del aire contaminado y por el uso de creosotas con bifenilos en la conservación de la madera) y la ingestión (debido a su uso como conservante de cítricos) pueden ser fuentes de exposición.

El bifenilo tiene propiedades bactericidas y fungicidas débiles. En estudios de toxicidad sobre organismos acuáticos de cuatro niveles tróficos, la concentración más baja sin efectos observados (NOEC) notificada para la especie más sensible (*Daphnia magna*) en pruebas

crónicas fue de 0,17 mg/litro. Se puede calcular una concentración sin efectos prevista (PNEC) de 1,7 ⋮g/litro mediante la aplicación de un factor de evaluación de 10, teniendo en cuenta las características de ecotoxicidad y destino en el medio ambiente de la sustancia. No se dispone de datos válidos sobre efectos tóxicos en organismos y ecosistemas terrestres, que se podrían utilizar para la evaluación del riesgo.

Debido a la falta de datos de otras partes del mundo, se realizó en Alemania una evaluación del riesgo de muestra. A partir de las concentraciones medias en los ríos alemanes en los años noventa, la relación entre la concentración prevista en el medio ambiente (PEC) y la PNEC se calcula que es #0,29. Una razón PEC/PNEC <1 indica que no cabe prever un riesgo importante para el medio ambiente.