

4-Phenylcyclohexene
[CASRN 4994-16-5]

Review of Toxicological Literature

July 2002

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Executive Summary

Nomination

4-Phenylcyclohexene was nominated once for toxicological studies in 1990 and again in 2001 by private individuals. The basis for nomination was its presence in indoor environments, primarily as a result of carpet emissions, and concern for possible neurotoxic and genotoxic effects.

Nontoxicological Data

Analysis and Physical-Chemical Properties

4-Phenylcyclohexene (4-PCH) from carpet samples was extracted with dichloromethane (methylene chloride) and determined by gas chromatography/mass spectrophotometry analysis of the extracts. It was alternatively determined by head-space technique utilizing triple quadruple MS. Indoor air was analyzed by GC with flame ionization detection.

4-PCH is a colorless liquid. Its saturation concentration in air is 79 ppm (510 mg/m³) at 21 °C, 760 mm Hg. It has a human odor threshold of 2 µg/m³ (0.3 ppb).

Commercial Availability, Production, and Uses

4-PCH forms as an undesirable byproduct during styrene-butadiene copolymerization as a Diels-Alder addition product of styrene and butadiene when conditions are not optimum. Average 4-PCH concentrations in styrene-butadiene rubber (SBR)-backed carpets decreased from 250 ppm (250 mg 4-PCH/kg carpet) in the late 1980s to less than 90 ppm by 1994, with its concentration being nondetectable in some samples.

4-PCH is apparently produced intentionally in only small quantities for research purposes and as an analytical standard. No commercial uses were identified for 4-PCH.

Environmental Occurrence and Persistence

Installed Carpets Constructed with Styrene-Butadiene Latex

4-PCH is considered to be a common semivolatile organic contaminant found in the built environment. It was one of the 12 most frequently occurring volatile organic chemicals (VOCs) emitted by 19 carpets backed by SBR latex. In one study, 4-PCH was the most abundant of ten VOCs found in headspace emissions from carpet constructed of nylon with a laminated fabric backing. The levels are not mentioned in this review.

4-PCH is the major odorant VOC associated with new carpets and is commonly found with styrene and 4-vinylcyclohexene (4-VCH), a butadiene dimer. The SBR latex adhesive for binding carpets' secondary backing is generally considered as the primary source of 4-PCH.

Other Sources

4-PCH might be present in emissions from production of SBR latex, although it is not mentioned in the process description for manufacture of SBR latex in the U.S. Environmental Protection Agency (U.S. EPA) report that developed emission factors for industries producing or using butadiene. For example, in field monitoring studies of two facilities that coated carpets with SBR latex for precoat and adhesive applications to nylon 6 and nylon 6,6 carpets, 4-PCH and 4-VCH were detected in the stack emissions as well as the listed Hazardous Air Pollutants (HAPs)

styrene and cumene. Such a carpet-coating plant has the potential to emit 60 tons VOCs per year (54 Mg/yr) when operating at its maximum production rate, with a total VOCs emission factor of 400 ± 130 mg per square yard of carpet. The industry average production rate may not be much more than half the maximum rate used in the calculation. Total U.S. carpet production was about 1.6×10^9 square yards ca. 1998.

No other industry was identified in the literature search as producing 4-PCH emissions.

Air concentrations measured in buildings after the installation of new carpet ranged from 0.3 to 2.6 ppb ($2 \mu\text{g}/\text{m}^3$ to $17 \mu\text{g}/\text{m}^3$).

Reactions with Ozone

4-PCH and other volatile carpet compounds react with ozone (O_3) at levels often found in indoor air to produce formaldehyde (HCHO) and C_5 - C_{10} aldehydes. Subsequently, the concentrations of alkenes such as styrene, 4-VCH, and 4-PCH in the carpet emissions fall. Samples of two carpets (one nylon pile and the other olefin-nylon) with polypropylene secondary backings affixed by SBR latex adhesives were studied in a stainless steel chamber. After 167 to 168 hours, 4-PCH concentrations were 3.1 ppb and 3.9 ppb ($20 \mu\text{g}/\text{m}^3$ and $25 \mu\text{g}/\text{m}^3$). At hour 194, after chamber exposure of sample 1 to ozone concentrations up to 409 ppb ($803 \mu\text{g}/\text{m}^3$) over about 37 hours, VOC concentrations increased, but the 4-PCH concentration had decreased to 0.14 ppb ($0.91 \mu\text{g}/\text{m}^3$). At a lower ozone concentration of about 30 ppb (about $60 \mu\text{g}/\text{m}^3$), the 4-PCH concentration from the second sample at hour 197 was reduced to 1.5 ppb ($9.7 \mu\text{g}/\text{m}^3$). In both experiments, 4-PCH concentrations climbed within 24 hours after ozone exposure ceased—from 0.14 ppb at hour 194 to 2.5 ppb at hour 217 (0.91 to $16 \mu\text{g}/\text{m}^3$) (sample 1) and from 1.5 ppb at hour 197 to 3.3 ppb at hour 223 (9.7 to $21.6 \mu\text{g}/\text{m}^3$) (sample 2). The authors concluded that 4-PCH apparently reacted with ozone to form other volatile products.

Human Exposure

Exposure to the general population is possible as a result of emission of 4-PCH from carpets and other SBR latex products in indoor environments. Occupational exposure is possible where SBR latex and carpets with SBR latex adhesive are manufactured or installed.

A single study quantifying levels of personal exposure to 4-PCH was identified. The second German Environmental Survey in the Western part of the country (GerES II) surveyed the personal exposure to VOCs of 113 adults between the ages of 25 to 69. Sampling was done with diffusive badge-type samplers close to the breathing zone. A questionnaire asked the pattern of specific room occupation, household characteristics, occupation, and lifestyle. The geometric mean of 4-PCH concentration to which the subjects had been exposed was $4.7 \mu\text{g}/\text{m}^3$ (0.73 ppb), with a range of $4.4 \mu\text{g}/\text{m}^3$ to $4.9 \mu\text{g}/\text{m}^3$ (0.68 ppb to 0.76 ppb).

Regulatory Status

No regulatory information was found in the Code of Federal Regulation titles 21, 29, and 40.

A letter to a consumer from the Consumer Product Safety Commission (CPSC) dated January 27, 1988, describes the Federal Hazardous Substances Act (FHSA 15 U.S.C. sec. 1261 et seq.) that requires household substances to be labeled if they contain “hazardous substances” and

authorizes the commission to ban any household product containing a hazardous substance if the commission decides that is the best way to protect the health and safety of the public adequately and the Consumer Product Safety Act (CPSA, 15 U.S.C. sec. 2051 et seq.), which authorizes the commission to eliminate or ameliorate “unreasonable risks of injury” connected with consumer products and to order that corrective action be taken with hazardous products. The letter did not mention how these laws were applied specifically to 4-PCH.

The U.S. EPA rejected a citizen’s petition of December 1989 to regulate the emission of 4-PCH because the toxicological data available did not support the assertions made in the petition.

In April 1990, U.S. EPA Administrator William Reilly denied a TSCA Section 21 petition from a U.S. EPA employee union whose members complained of health problems after a building renovation. Instead, he promised a voluntary program for reducing indoor air emissions. The petition had asked to limit 4-PCH levels and to require manufacturers to conduct studies and to achieve less-than-parts-per-billion levels, altering the process of manufacture when necessary.

In September 1991, the U.S. EPA signed memoranda of understanding (MOUs) with the Carpet Cushion Council, the Styrene Butadiene Latex Manufacturers Council (SBLMC) and the Floor Covering Adhesive Manufacturers Committee, covering the testing procedures to measure total VOC emissions from their products. The SBLMC announced a voluntary limit of 300 ppm (1,940 mg/m³) on levels of 4-PCH effective July 1, 1992.

VOCs from carpets were removed from the Toxic Substances Control Act (TSCA) master testing list for a voluntary testing agreement when testing was completed in 1996.

Toxicological Data

Human Data

In a German study of indoor air, 4-PCH was present in the air samples and rated as “odour active.” The researchers said such chemicals “contribute to poorly perceived indoor air quality.” Exposure to low levels of 4-PCH and other emission products (levels not provided) has been associated with headaches, eye irritation, and nausea.

4-PCH is among new carpet emissions purportedly associated with adverse human health effects. The CPSC and the U.S. EPA began a study of carpet emissions in 1989. However, neither agency has established a causal link between reported health effects and new carpets. The CPSC collected complaint reports related to VOCs from new carpet installations from 355 residents in 206 households between 1988 and early 1990 in the United States. The symptoms, which began either immediately or within several days of new carpet installation, included upper respiratory tract problems, eye irritation, headaches, rashes, fatigue, difficulty concentrating, headaches, nausea, excessive thirst, dry mouths, burning of eyes, nose and sinuses, incoherent speech, depression, sore throat, itchy skin, burning feet and legs, chronic rhinitis, and lips that were dry, puffy, and irritated. There was no control group reported, and relative incidences were not reported. In addition to some of these complaints, unsteady gait was named among U.S. EPA workers in a newly renovated building.

Styrene-butadiene formulations caused slight irritation to human skin but no evidence of skin sensitization.

Chemical Disposition, Metabolism, and Toxicokinetics

In the absence of metabolism data for 4-PCH, some data are mentioned on some of its metabolites and analogs: 1-phenylcyclohexene (1-PCH), cyclohexene, cyclohexene oxide (CHO), biphenyl, and 4-VCH.

Acute Exposure

The LD₅₀ for Fischer 344 (F-344) rats exposed to airborne 4-PCH for six hours was greater than the highest dose tested, 60 ppm (400 mg/m³). The LD₅₀ for rats for oral administration of a single dose of 4-PCH was greater than 2 g/kg (0.01 mol).

Short-Term and Subchronic Exposure

Male Swiss-Webster mice (five weeks old, 20 per concentration) were administered 0 or 62 ppm (0 or 401 mg/m³) 4-PCH (97.2 percent pure), by whole-body exposure for six hours per day, nine consecutive days, followed by in-life observations and neurohistopathology on selected tissues. No treatment-related central nervous system lesions were found.

Male and female Swiss-Webster mice (five weeks old, 20 per sex per concentration) were administered 0, 7, 18, or 71 ppm (0, 50, 120, 460 mg/m³) 4-PCH (97.2 percent pure), by whole-body exposure for six hours per day, nine consecutive days. Fifty percent of the animals underwent in-life observations while 50 percent underwent neurological evaluations. No clear treatment-related effects were noted despite exposure at near-saturated atmosphere. No effects could be definitively related to 4-PCH based on in-life parameters, functional observational battery, motor activity, or gross pathological or histopathological examination of organs and tissues.

Male and female F-344 rats (6 to 8 weeks old, ten per sex per concentration) were administered 0, 1, 10, or 50 ppm (0, 7, 70, or 300 mg/m³) 4-PCH (98 percent pure) by whole-body exposure for two weeks, six hours per day, five days per week, for nine exposures. Animals were observed each day, and body weights were recorded periodically. All animals were sacrificed one day after the last exposure. The time weighted average mean daily analytical concentrations were 1.2, 10.0, and 49.8 ppm. No treatment-related clinical signs were observed. All rats survived until the necropsy. Hematologic parameters were not altered following exposures to 4-PCH. Urinalysis revealed a statistically significant decrease in the specific gravity (1.030 ± 0.011) for females exposed to 50 ppm relative to the control group (1.043 ± 0.015); authors concluded that this was of no toxicologic significance as it was within the range of historical control values. The statistically significant increase in mean relative brain weight for males exposed to 50 ppm was thought to be a reflection of the non-significant reduction in terminal fasted body weight. No treatment-related gross or microscopic changes were observed.

Cytotoxicity

A commercial styrene-butadiene formulation was tested on cultured mouse fibroblast cells and was shown to be noncytotoxic.

Reproductive and Teratological Effects

Female B6C3F₁ mice (28 days old, 15 per dose group) were administered 3.0 or 6.0 mmol/kg (475 or 950 mg/kg) 4-PCH (98% pure) intraperitoneally (i.p.), once a day for 30 days. The negative control group was dosed with sesame seed oil. Animals were sacrificed on the first day of diestrus after the last dose. Neither dose of 4-PCH had any effect on follicle numbers compared to the sesame oil control group. Light microscopic examination of 4-PCH-treated ovaries failed to detect any histologic changes. The number of estrous cycles per 30 days decreased from 4.8 in the control group to 3.2 in the higher 4-PCH-dose group. The number of estrous cycles returned to control values within 30 days of treatment discontinuation.

Immunotoxicology

4-PCH was applied dermally to ten male Hartley albino guinea pigs once a week for three weeks. The test material was placed in a naïve area of the animals 14 days after the final induction application. DER331 epoxy resin in dipropylene glycol monomethyl ether (DPGME) was applied to one group as a positive control. Twenty-four and 48 hours later, they were graded on induction response. The non-irritating concentration of 4-PCH used for induction was 10 percent. The same concentration was applied for the challenge phase and caused no response.

Toxicity studies of commercial styrene-butadiene formulations containing 4-PCH showed it caused slight skin irritation and swelling in rabbits, guinea pigs, and rats, with no evidence of permanent skin damage or of skin sensitization.

Data Not Located

No studies of 4-PCH pertaining to chronic exposure, synergistic/antagonistic effects, carcinogenicity, initiation-promotion, anticarcinogenicity, genotoxicity, cogenotoxicity, and antigenotoxicity were located.

Other Data

The 1996 CPSC study tested 17 compounds associated with carpet and carpet cushion emissions for sensory irritation in mice, determined by measuring a concentration-dependent decrease in respiration rate. Sensory irritation for each compound was compared based on the levels predicted to cause 50 percent, 20 percent, and 12 percent respiratory depression, or RD₅₀, RD₂₀ and RD₁₂, measured by the American Society for Testing and Materials bioassay designation E (ASTM E). Pulmonary irritation was determined by measuring a post-expiratory bradypnea. The average respiratory frequency was based on percentage of baseline frequency. Mice were exposed to vapors, one chemical at a time, head only, for 60 minutes. Of nine exposures, the lowest, 23 mg/m³ did not significantly depress respiration. The 4-PCH RD₅₀ was 319 mg/m³ (49 ppm), the RD₂₀ was 59.6, and the RD₁₂ was 38.1. Respiratory depression and onset of sensory irritation were relatively rapid. At all exposures to 4-PCH, except at the lowest concentrations, there was mild recovery toward baseline during the exposure period. After exposure, there was recovery toward baseline for all exposures.

Out of 11 chemicals tested for irritation response, 4-PCH was the least irritating, with an RD₂₀ of 9.2 ppm (59.6 mg/m³). The most irritating of the chemicals was 2-methylnaphthalene with an RD₂₀ of 0.4 ppm (2.5 mg/m³). Installation of 4-PCH in surgically exposed tracheas of rats yielded pulmonary effects. This result is not indicative of inhalation exposure to 4-PCH.

Commercial styrene-butadiene formulations that contain 4-PCH caused temporary corneal injury or irritation in rabbits, but caused no permanent damage.

Structure-Activity Relationships

Selected toxicity information for the structurally-related compounds cyclohexene, 1-PCH, CHO, biphenyl, and 4-VCH is summarized in this report.

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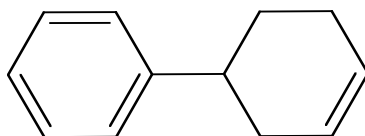
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1.0 Basis for Nomination

4-Phenylcyclohexene was nominated for toxicological studies in 1990 and again in 2001 by private individuals. The basis for nomination was its presence in indoor environments, primarily as a result of carpet emissions, and concern for possible neurotoxic and genotoxic effects.

2.0 Introduction

4-Phenylcyclohexene
[4994-16-5]



2.1 Chemical Identification and Analysis

4-Phenylcyclohexene (4-PCH) ($C_{12}H_{14}$; mol. wt. = 158.24) is also called:
Benzene, 3-cyclohexen-1-yl- (6CI, 8CI, 9CI)
Benzene, (3-cyclohexen-1-yl)- (7CI)
(3-Cyclohexen-1-yl)benzene

4-PCH from carpet samples was extracted with dichloromethane (methylene chloride) and determined by gas chromatography/mass spectrophotometry (GC/MS) analysis of the extracts. It was alternatively determined by head-space technique utilizing triple quadruple MS. Indoor air was analyzed by GC with flame ionization detection (Singhvi et al., 1990).

A study showed GC/MS to be a good method of determining ambient air contaminants, at concentrations in the range of 0.2 ppbv ($1.3 \mu\text{g}/\text{m}^3$) at the 99 percent confidence level including 4-PCH, in ambient air (LoSurdo et al., 1995).

An OVM-3500 diffusive sampler close to the breathing zone was used to collect volatile organic compounds. At the end of seven days, the collecting surface was covered with a lid, wrapped tightly in aluminum foil, then sent to a laboratory (Hoffman et al., 2000). The air sample was analyzed by GC according to German VDI guideline 3482/4 (VDI, 1984; cited by Hoffman et al., 2000). The procedure involves sample collection in activated carbon, desorption of CS_2 and separation using a nonpolar capillary GC column, and identification by retention indices and by the retention index differences. Another aliquot of the sample was analyzed on another gas chromatograph possessing a column of a slightly different polarity (Hoffman et al., 2000).

A separation column ensemble with tunable and programmable retention characteristics was used to analyze an air mixture containing 42 chemicals, including 4-PCH (Grall et al., 2001). The compound has also been characterized by GC/matrix isolation/Fourier transform infrared spectroscopy (GC/MI/FT-IR). Impurities were identified as two isomers of PhC_6H_9 and two isomers of $\text{C}_{12}\text{H}_{18}$ (Dow Chemical Co., 1989b).

4-PCH impurities were tentatively identified as two isomers of phenylhexene and two isomers of C₁₂H₁₈ (Beekman et al., 1996).

2.2 Physical-Chemical Properties

| Property | Information | Reference(s) |
|---|---|--|
| Physical State | Colorless liquid | Dow Chemical Co. (1989a) |
| Odor threshold | 2 µg/m ³ (0.3 ppb) threshold | Jensen and Wolkoff (1996); cited by Wolkoff (1998) |
| Conversion factor (ppb to µg/m ³) | 6.47 | As calculated. |
| Irritation threshold in guinea pigs | 50% 4-PCH in DPGME | Dow Chemical Co. (1989b) |
| Boiling Point °C | 242.9 | Dow Chemical Co. (1989b) |
| Melting Point °C | n.p. | |
| Density (g/cm ³ at 20 °C) | 0.99 | CPSC (1996) |
| Water Solubility | 0.01 mol/L | Registry (2002) |
| Vapor pressure (at 25 °C) | 9.6 x 10 ⁻² mm Hg Torr | Dow Chemical Co. (1989b) |
| Saturation concentration in air (at 21 °C, 760 mm Hg) | 79 ppm (510 mg/m ³) | Beekman et al. (1996) |
| Other Solubilities | Carbon tetrachloride, carbon disulfide | HODOC (2002) |
| Log of the octanol-water partition coefficient (log K _{OW} ; LogP) | 4.281 ± 0.201 | Registry (2002) |
| UV absorption coefficient in ethyl alcohol | 248 nm (776 m ² /mol) | HODOC (2002) |

Abbreviations: DPGME = dipropylene glycol monomethyl ether; n.p. = not provided.

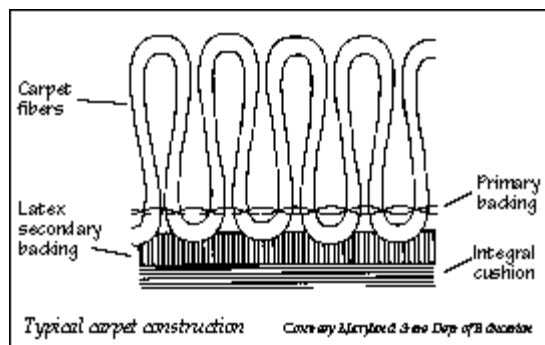
2.3 Commercial Availability

ChemSampCo. of Trenton, NJ, supplies 4-PCH, 98 percent purity, in 5-g quantities (CHEMCATS, 2002; ChemSampCo., 2001).

3.0 Production Processes

4-PCH forms as an undesirable byproduct during styrene-butadiene copolymerization as a Diels-Alder addition product of styrene and butadiene when conditions are not optimum (Zellweger et al., 1997; BuildingGreen, Inc., 1994). Average 4-PCH concentrations in styrene-butadiene rubber (SBR)-backed carpets decreased from 250 ppm (250 mg 4-PCH/kg carpet) in the late 1980s to less than 90 ppm by 1994, with its concentration being nondetectable in some samples.

In a typical carpet construction, after dyeing and drying, the carpet is coated with a layer of adhesive (usually SBR latex filled with calcium carbonate) to lock fibers and tufts in place as well as to affix a secondary backing; this process enhances strength and stability of the carpet. Woven carpets require less backing due to their greater stability. The primary carpet backing is usually polypropylene into which the pile yarns of a tufted carpet are stitched. The most common carpets in 1994 had nylon face fibers. Secondary backings are usually woven polypropylene, but may be jute or attached cushioning. Some carpets may be latex coated without a secondary backing. In inexpensive carpets, thick SBR latex coatings serve as the secondary backing. In those cases, up to two pounds SBR latex may be used per square yard of carpet (U.S. EPA OAQPS, 1998b; BuildingGreen, Inc., 1994).



Source: BuildingGreen, Inc. (1994)

4.0 Production and Import Volumes

Based on package sizes, 4-PCH is apparently produced intentionally in only small quantities for research purposes and as an analytical standard.

5.0 Uses

No commercial uses were identified for 4-PCH.

6.0 Environmental Occurrence and Persistence

6.1 Sources of Emissions

6.1.1 Installed Carpets Constructed with Styrene-Butadiene Latex

4-PCH is considered to be a common semivolatile organic contaminant found in the built environment (Brown et al., 1994; Krause et al., 1987; both cited by Grall et al., 2001; Molhave et al., 1997). It was one of the 12 most frequently occurring volatile organic compounds (VOCs) emitted by 19 carpets backed by SBR latex. All 19 emitted styrene and 4-PCH and 16 emitted 4-vinylcyclohexene (4-ethenylcyclohexene, referred to here as 4-VCH) (summary based on four reports cited in a review by Dietert and Hedge, 1996). In a study by Siefert et al. (1989; cited by Dietert and Hedge, 1996), 4-PCH was the most abundant of ten VOCs found in headspace emissions from carpet constructed of nylon with a laminated fabric backing. The levels are not mentioned in this review.

4-PCH is the major odorant VOC associated with new carpets and is commonly found with styrene and 4-VCH, a butadiene dimer. The SBR latex adhesive for binding carpets' secondary backing is generally considered as the primary source of 4-PCH (Weschler et al., 1992).

As described in subsection 6.3.2, Chamber Studies, the carpet industry has substantially reduced organic emissions since 1992 (Carpet & Rug Institute, 2002). Outgassing of chemicals from carpet has been reduced by two-thirds (Bez, 1994).

6.1.2 Other Sources

4-PCH might be present in emissions from production of SBR latex, although it is not mentioned in the process description for manufacture of SBR latex in the U.S. Environmental Protection

Agency report that developed emission factors for industries producing or using butadiene (U.S. EPA OAQPS, 1996). For example, in field monitoring studies of two facilities that coated carpets with SBR latex for precoat and adhesive applications to nylon 6 and nylon 6,6 carpets, Mulholland and coworkers detected 4-PCH and 4-VCH in the stack emissions as well as the listed Hazardous Air Pollutants (HAPs) styrene and cumene (Mulholland, 1999 project description). (No related Mulholland journal publications or government reports were identified in April 2002 searches of NTIS and CAPLUS or in Dr. James A. Mulholland's list of publications at the Georgia Institute of Technology's web site.) Such a carpet-coating plant has the potential to emit 60 tons VOCs per year (54 Mg/yr) when operating at its maximum production rate with a total VOCs emission factor of 400 ± 130 mg per square yard of carpet. The industry average production rate may not be much more than half the maximum rate used in the calculation (comments by T. Virgo at the Third PMACT [Presumptive Maximum Achievable Control Technology] Meeting for Fabric, Coating, and Dyeing) (U.S. EPA OAQPS, 1998a). Total U.S. carpet production was about 1.6×10^9 square yards ca. 1998 (U.S. EPA OAQPS, 1998b).

4-PCH may be found in emissions from other industrial processes that use SBR latex; however, no other industry was identified in the literature search.

6.2 Room Air Monitoring Studies

6.2.1 Field Studies After New Carpet Installation

Air concentrations measured in buildings after the installation of new carpet ranged from 0.3 to 2.6 ppb ($2 \mu\text{g}/\text{m}^3$ to $17 \mu\text{g}/\text{m}^3$) (Vogelmann et al., 1988; cited by Beekman et al., 1996).

After renovations at the U.S. Environmental Protection Agency's headquarters in southwest Washington, DC, comprising two office towers separated by a shopping mall, health complaints prompted an industrial hygiene survey. Air-exchange rates were as low as 0.2/hour, and 4-PCH concentrations were 0.9 ppb ($6 \mu\text{g}/\text{m}^3$) in the offices and 1.5 ppb ($9.7 \mu\text{g}/\text{m}^3$) in the mall area, where new carpet had been installed. 4-PCH levels at the time of carpet installation were estimated at 5 ppb to 15 ppb ($30 \mu\text{g}/\text{m}^3$ to $97 \mu\text{g}/\text{m}^3$) (Welch and Sokas, 1992). The jute-backed carpeting used originally contained 70 ppb 4-PCH ($70 \mu\text{g}/\text{kg}$ carpet). Office air concentrations of 3.5 to 6.5 ppb ($23 \mu\text{g}/\text{m}^3$ to $42 \mu\text{g}/\text{m}^3$) 4-PCH after installation were reduced by improved ventilation (Singhvi et al., 1990).

After installation was completed of a new nylon carpet with SBR latex adhesive that had been shipped from the carpet mill within the previous six days, 4-PCH and styrene concentrations were monitored at 12- or 24-hour intervals for the next seven weeks. (Carpet covered 93 m^2 of the total 132-m^2 area, and the three-story townhouse's volume was 400 m^3). The day before carpet installation, the 4-PCH concentration was zero (ventilation rate 9.6/hr). Two days after installation at a ventilation rate of 7.3/hr, the 4-PCH concentration was 1.6 ppb ($10 \mu\text{g}/\text{m}^3$) and its emission rate was $320 \mu\text{g}/\text{m}^2/\text{hr}$. The maximum 4-PCH concentration, 5.1 ppb ($33 \mu\text{g}/\text{m}^3$) was measured on day 6 at a ventilation rate of 1.1/hr, but the emission rate at that time was only $150 \mu\text{g}/\text{m}^2/\text{hr}$. By days 40 to 52, the 4-PCH concentration was 3.2 ppb ($21 \mu\text{g}/\text{m}^3$) with an emission rate on day 52 of $59 \mu\text{g}/\text{m}^2/\text{hr}$ at a ventilation rate of 0.7/hr (Hodgson et al., 1993).

6.2.2 Field Studies Unrelated to New Carpet Installation

4-PCH was identified as one of the odorant chemicals in air sampled from offices in two buildings in Berlin, Germany. (The others were *n*-propylbenzene and 1-octen-3-ol.) The GC/FID apparatus allowed a human “sniffer” to determine if each of the separated compounds had an odor. Concentrations were not provided, but based on the graphs and the relative areas under the curve, 4-PCH concentrations were higher in the room with metal and synthetic resin furnishings than in the room with wood furnishings (Schleibinger et al., 2001a).

4-PCH was found in only four of 246 room air samples collected in Germany between 1988 and 1999. The mean concentration was 1 $\mu\text{g}/\text{m}^3$, and the maximum concentration was 5 $\mu\text{g}/\text{m}^3$. Concentrations were most frequently below the detection limit of 1 $\mu\text{g}/\text{m}^3$. No information was provided on concentration trends in the time period covered (Schleibinger et al., 2001b).

4-PCH was one of the most abundant compounds tentatively identified in a composite of air samples collected from 757 Canadian homes ca. 1992. The tentative identification was based on scan-mode operation of a GC-MSD (mass selective detector) apparatus (Otson et al., 1994).

In a study of VOC levels in smoking and nonsmoking environments in the greater Philadelphia area (Heavner et al., 1996), the 4-PCH concentrations, from highest to lowest, were as follows:

- in homes of smokers, a mean of 0.13 $\mu\text{g}/\text{m}^3$ (0.02 ppb) and a maximum of 1.87 $\mu\text{g}/\text{m}^3$ (0.289 ppb);
- in homes of nonsmokers, a mean of 0.06 $\mu\text{g}/\text{m}^3$ (0.009 ppb) and a maximum of 1.29 $\mu\text{g}/\text{m}^3$ (0.199 ppb);
- in workplaces where smoking was permitted, a mean of 0.07 $\mu\text{g}/\text{m}^3$ (0.01 ppb) and a maximum of 0.64 $\mu\text{g}/\text{m}^3$ (0.099 ppb);
- in nonsmoking workplaces, a mean of 0.04 $\mu\text{g}/\text{m}^3$ (0.006 ppb) and a maximum of 0.63 $\mu\text{g}/\text{m}^3$ (0.097 ppb).

6.3 Experimental Studies

6.3.1 Non-chamber Studies

Direct thermal desorption studies of 15 SBR-latex-backed carpet samples found 4-PCH amounts in the range 3.49 to 45.0 ng/mg carpet (3.49 to 45.0 ppm) in 11 samples (mean 18.8 ng 4-PCH/mg carpet when present) (Lee et al., 1999). A U.S. EPA-sponsored study in which commercial-grade carpet samples were extracted with methylene chloride found 4-PCH in concentrations up to 115 $\mu\text{g}/\text{g}$ carpet (115 ppm). Carpet samples had been received in sealed packages. By headspace sampling, 4-PCH was found in six of the seven carpet samples, as a major (3), minor (2), or trace component (1). Styrene was present in the three samples in which 4-PCH was a major component (Pleil and Whiton, 1990).

Nylon 6,6 pile carpet pieces were coated with freshly compounded SBR latexes containing either 700 ppm w/w (dry resin basis) 4-PCH (latex A) or 250 ppm 4-PCH (latex B) to adhere a polypropylene secondary backing material to give carpet samples containing about 60 or 20 ppm 4-PCH, respectively. When the freshly prepared samples were heated in ovens with three air exchanges per minute, the removal rates after about 10 minutes were faster with increasing temperatures of 225 to 275 °F (107 to 135 °C) and depended little on 4-PCH content. Carpet

samples using latex A or latex B were depleted of 4-PCH after 1 hour at all three temperatures used. At an oven temperature of 275 °F (135 °C), more than 50 percent of the 4-PCH in the two carpet samples was released within 10 minutes. At 225 °F (107 °C), only 16 to 20 percent was released from the samples at 10 minutes. Under forced air conditions (1,500 linear feet per minute; 76 cm/s), the two carpet samples released about 90 percent available 4-PCH in 10 minutes, but the unexposed sample released less than 30 percent in 10 minutes (SBLMC, 1990a).

6.3.2 Chamber Studies

Several publications have reported the results of climate-controlled chamber studies of carpet emissions in which temperature, ventilation rate, turbulence, and/or relative humidity were sometimes varied. The effects on semivolatile compounds like 4-PCH were not readily generalized, with results among the studies sometimes appearing to conflict. The studies described in this subsection are arranged in approximately chronological order, with the exception of the Carpet & Rug Institute testing program description at the end.

4-PCH emissions from SBR latex-backed carpets decreased by 63 percent within one week in chamber tests, which represented a half-life of 2.9 days. The 4-PCH emission factor at hour 24 after testing began was 28 $\mu\text{g}/\text{m}^2/\text{hr}$ (Black et al., 1991; cited by Dietert and Hedge, 1996). In a similar study, the 4-PCH-emission factor from eight SBR latex-backed nylon carpets averaged 89 $\mu\text{g}/\text{m}^2/\text{hr}$ at hour 24 (Black, 1990; cited by Dietert and Hedge, 1996). Conditions were not provided in the review. The 1991 study may have been of a room installation; the review stated that the emission factor was for a carpet and flat pad on concrete and that the average was estimated by the reviewers from graphed data.

Emission rates of 4-PCH from carpet in an environmental chamber at 25 °C, 50 percent relative humidity, and air velocity of 0.10 m/s decreased from 33 $\mu\text{g}/\text{m}^2/\text{hr}$ in the first hour to 20 $\mu\text{g}/\text{m}^2/\text{hr}$ in the 24th hour (Hawkins et al., 1992).

Under static chamber conditions (without air exchange), temperature changes impact concentrations observed in carpet emissions, whereas the effect of relative humidity is negligible. In chamber experiments under dynamic conditions (well mixed with a defined chamber loading) at 23 °C and 45 percent relative humidity, concentrations of 4-PCH and other semivolatile compounds decreased only slowly over a time scale of months in contrast to the gas-phase concentrations of volatile compounds, which peaked within an hour and decreased to less than 2 percent within 60 hours. Under these conditions, air concentrations were independent of chamber size, wall material, and air velocity. High air-exchange rates tended to increase mass transfer to the gas phase. In the experiments, SBR-backed polyamide (nylon) carpets were used within six weeks of delivery from the mill to a German wholesaler. About 80 percent of German carpets were of the type used (Sollinger et al., 1993).

Three samples of two carpets were evaluated for VOC emissions in a chamber at 22.8 to 23.5 °C and 46.5 to 50.2 percent relative humidity with air velocity 6.5 to 9 cm/s. The range of mean 4-PCH emission rates ranged from 64.5 $\mu\text{g}/\text{m}^2/\text{hr}$ to 85.1 $\mu\text{g}/\text{m}^2/\text{hr}$ at hour 24, declining to 48.5 $\mu\text{g}/\text{m}^2/\text{hr}$ to 64.0 $\mu\text{g}/\text{m}^2/\text{hr}$ at hour 168. Other VOCs quantified from the samples were alkylbenzenes and styrene at similar concentrations. About 20 percent of the total 4-PCH (by mass) emitted within 168 hours was emitted in the first 24 hours (Hodgson et al., 1993).

Zellweger et al. (1997) reported that 4-PCH was emitted at the rate of 3 to 32 $\mu\text{g}/\text{m}^2/\text{hr}$ (mean of 15 $\mu\text{g}/\text{m}^2/\text{hr}$ when present) for four of five newly manufactured carpet samples while styrene was emitted from only three of the four samples at 1 to 8 $\mu\text{g}/\text{m}^2/\text{hr}$. 4-PCH was not detected in two SBR-backed carpet samples of unknown history that had been purchased retail.

Wolkoff (1998) studied the effects of air velocity, temperature, humidity, and air on long-term emissions from latex-backed nylon carpet samples that had been stored in inert and diffusion-tight packaging at 15 °C since receipt from the manufacturer. The 4-PCH concentration was markedly elevated at the lowest air velocity (1 cm/s) during the first two weeks of the experiment and generally had a higher concentration/time profile at the two highest air velocities (5 and 9 cm/s) during the first week. Measurements were near the limit of detection. The 4-PCH concentrations decreased to 0.5 $\mu\text{g}/\text{m}^3$ (0.08 ppb) within one week at 60 °C and within about two weeks at 23 and 35 °C. Concentrations of 4-PCH were only slightly affected by relative humidity during the first week with a negligible effect after two to four weeks. Because of the low concentration of 4-PCH, reactivity under aerobic vs. anaerobic conditions was not apparent (Wolkoff, 1998).

The effects of local air velocity and turbulence on the emission rates of 4-PCH, nonane and decane, and total VOCs were reported in a chamber study in which the samples of carpets and adhesives were common to homes and office buildings. The chamber temperature was 23 ± 1.3 °C and the relative humidity was 45.5 ± 3 percent. In the initial 30 hours after jute-backed nylon-olefin carpet samples were placed in a stainless-steel chamber, increasing the velocity of air blowing over the sample assembly increased total VOC emission rates. The emission rates declined sharply during that time and were low for the remaining 200 hours. However, 4-PCH concentrations, which were not detected in the first 50 hours, were very low compared to those of nonane and decane. The highest air concentration of 4-PCH was 24 $\mu\text{g}/\text{m}^3$ (3.7 ppb); the highest for nonane and decane were 40.2 mg/m^3 (6.23 ppm) and 50 mg/m^3 (7.75 ppm), respectively. This was an atypical experiment in which emissions from the freshly applied adhesive used to affix the carpet sample to a concrete substrate before sample insertion in the chamber were much higher than emissions from the carpet sample. The cement adhesive was apparently not a source of 4-PCH (Low et al., 1998).

The Carpet & Rug Institute (CRI) established a labeling program to identify low VOC-emitting carpets that have been found by an independent laboratory to meet the following criteria expressed as maximum emission factor in micrograms per square meter per hour:

- Total VOCs 500
- Styrene 400
- Formaldehyde 50
- 4-PCH 50

The CRI Indoor Air Quality Carpet Testing green-and-white logo is displayed on low-VOC carpet samples in U.S. show rooms. Product re-testing occurs quarterly. Testing methodology conforms to “ASTM (American Society for Testing and Materials (ASTM) method D 5116—Guide for Small-Scale Environmental Chamber Determinations of Organic Emissions from Indoor Materials/Products” (Carpet & Rug Institute, 2002).

INDOOR AIR QUALITY CONSUMER INFORMATION

IMPORTANT HEALTH INFORMATION:
SOME PEOPLE EXPERIENCE ALLERGIC OR FLU-LIKE SYMPTOMS, HEADACHES, OR RESPIRATORY PROBLEMS WHICH THEY ASSOCIATE WITH THE INSTALLATION, CLEANING, OR REMOVAL OF CARPET OR OTHER INTERIOR RENOVATION MATERIALS. IF THESE OR OTHER SYMPTOMS OCCUR, NOTIFY YOUR PHYSICIAN OF THE SYMPTOMS AND ALL MATERIALS INVOLVED.


SENSITIVE INDIVIDUALS:
PERSONS WHO ARE ALLERGY-PHONE OR SENSITIVE TO ODORS OR CHEMICALS SHOULD AVOID THE AREA OR LEAVE THE PREMISES WHEN THESE MATERIALS ARE BEING INSTALLED OR REMOVED.

NOTE:
YOU CAN REDUCE YOUR EXPOSURE TO MOST CHEMICAL EMISSIONS WHEN CARPET AND OTHER INTERIOR RENOVATING MATERIALS ARE INSTALLED, CLEANED, OR REMOVED BY INCREASING THE AMOUNT OF FRESH AIR VENTILATION FOR AT LEAST 72 HOURS. (See Installation and Maintenance Guidelines or ask for Owner's Manual.)

INSTALLATION GUIDELINES:

- VACUUM OLD CARPET BEFORE REMOVAL
- VACUUM FLOOR AFTER CARPET AND PAD HAVE BEEN REMOVED
- ALWAYS VENTILATE WITH FRESH AIR (OPEN DOORS AND/OR WINDOWS, USE EXHAUST FANS, ETC.) DURING ALL PHASES OF INSTALLATION AND FOR AT LEAST 72 HOURS THEREAFTER
- IF ADHESIVES AND/OR PAD ARE USED, REQUEST THOSE WHICH HAVE LOW CHEMICAL EMISSIONS
- FOLLOW DETAILED INSTALLATION GUIDELINES FROM MANUFACTURER OR FROM CARPET AND RUG INSTITUTE

The manufacturer of this carpet participates in a program which seeks to develop ways to reduce emissions by testing samples of carpet. With fresh air ventilation, most carpet emissions are substantially reduced within 48-72 hours after installation.



FOR MORE INFORMATION: CARPET AND RUG INSTITUTE 800/882-8848

Source: BuildingGreen, Inc. (undated).

In these quarterly tests, emissions are measured 24 hours after manufacture. Program testing and most industry-sponsored research is done by Air Quality Sciences, Inc., Atlanta, GA. Testing began in 1992; at that time, only 80 percent of the carpets tested met the criteria, but marked improvements were noted by 1994 (BuildingGreen, Inc., 1994).

6.3.3 Reactions with Ozone

4-PCH and other volatile carpet compounds react with ozone (O_3) at levels often found in indoor air to produce formaldehyde (HCHO) and C_5 - C_{10} aldehydes. Subsequently, the concentrations of alkenes such as styrene, 4-VCH, and 4-PCH in the carpet emissions fall. Samples of two carpets (one nylon pile and the other olefin-nylon) with polypropylene secondary backings affixed by SBR latex adhesives were studied in a stainless steel chamber. After 167 to 168 hours, 4-PCH concentrations were 3.1 ppb and 3.9 ppb ($20 \mu\text{g}/\text{m}^3$ and $25 \mu\text{g}/\text{m}^3$). At hour 194, after chamber exposure of sample 1 to ozone concentrations up to 409 ppb ($803 \mu\text{g}/\text{m}^3$) over about 37 hours, VOC concentrations increased, but the 4-PCH concentration had decreased to 0.14 ppb ($0.91 \mu\text{g}/\text{m}^3$). At a lower ozone concentration of about 30 ppb (about $60 \mu\text{g}/\text{m}^3$), the 4-PCH concentration from the second sample at hour 197 was reduced to 1.5 ppb ($9.7 \mu\text{g}/\text{m}^3$). In both experiments, 4-PCH concentrations climbed within 24 hours after ozone exposure ceased—from 0.14 ppb at hour 194 to 2.5 ppb at hour 217 (0.91 to $16 \mu\text{g}/\text{m}^3$) (sample 1) and from 1.5 ppb at hour 197 to 3.3 ppb at hour 223 (9.7 to $21.6 \mu\text{g}/\text{m}^3$) (sample 2). The authors concluded that 4-PCH apparently reacted with ozone to form other volatile products (Weschler et al., 1992).

7.0 Human Exposure

4-PCH is among VOCs in new carpet emissions (Hawkins et al., 1992) and is associated with new carpet odor (Chakrabarti, 1989; cited by Beekman et al., 1996).

Exposure to the general population is possible as a result of emission of 4-PCH from carpets and other SBR latex products in indoor environments. Occupational exposure is possible where SBR latex and carpets with SBR latex adhesive are manufactured or installed.

A single study quantifying levels of personal exposure to 4-PCH was identified. The second German Environmental Survey in the Western part of the country (GerES II) surveyed the personal exposure to VOCs of 113 adults between the ages of 25 to 69. Sampling was done with diffusive badge-type samplers close to the breathing zone. A questionnaire asked the pattern of specific room occupation, household characteristics, occupation, and lifestyle. The geometric mean of 4-PCH concentration to which the subjects had been exposed was $4.7 \mu\text{g}/\text{m}^3$ (0.73 ppb) with a range of $4.4 \mu\text{g}/\text{m}^3$ to $4.9 \mu\text{g}/\text{m}^3$ (0.68 ppb to 0.76 ppb) (Hoffman et al., 2000).

8.0 Regulatory Status

No regulatory information was found in the Code of Federal Regulation titles 21, 29, and 40.

According to a letter to a consumer from the Consumer Product Safety Commission (CPSC) dated January 27, 1988, the Federal Hazardous Substances Act (FHSA 15 U.S.C. sec. 1261 et seq.) requires that household substances be labeled if they contain “hazardous substances” that are toxic, irritants, or strong sensitizers and that are toxic, irritants, or strong sensitizers and that may cause substantial personal injury or illness as a result of customary handling or use. The Act authorizes the commission to ban any household product containing a hazardous substance if the commission decides that is the best way to protect the health and safety of the public adequately (U.S. EPA, 1988). It mentions the Consumer Product Safety Act (CPSA, 15 U.S.C. sec. 2051 et seq.), which authorizes the commission to eliminate or ameliorate “unreasonable risks of injury” connected with consumer products and to order that corrective action be taken with hazardous products. The letter did not mention how these laws were applied specifically to 4-PCH (U.S. EPA, 1988).

The U.S. EPA rejected a citizen’s petition of December 1989 to regulate the emission of 4-PCH because the toxicological data available did not support the assertions made in the petition (Hawkins et al., 1992).

In April 1990, U.S. EPA Administrator William Reilly denied a TSCA Section 21 petition from a U.S. EPA employee union whose members complained of health problems after a building renovation. Instead, he promised a voluntary program for reducing indoor air emissions. The petition had asked to limit 4-PCH levels and to require manufacturers to conduct studies and to achieve less-than-parts-per-billion levels, altering the process of manufacture when necessary (Pesticide and Toxic Chemical News, 1990).

In September 1991, the U.S. EPA signed memoranda of understanding (MOUs) with the Carpet Cushion Council, the Styrene Butadiene Latex Manufacturers Council (SBLMC) and the Floor Covering Adhesive Manufacturers Committee, covering the testing procedures to measure total

VOC emissions from their products. The SBLMC announced a voluntary limit of 300 ppm (1,940 mg/m³) on levels of 4-PCH effective July 1, 1992 (Moore, 1991).

VOCs from carpets were removed from the Toxic Substances Control Act (TSCA) master testing list for a voluntary testing agreement when testing was completed in 1996 (U.S. EPA OPPT, 1996).

9.0 Toxicological Data

9.1 General Toxicology

9.1.1 Human Data

In a German study of indoor air, 4-PCH was present in the air samples and rated as “odour active.” According to the researchers, such chemicals “contribute to poorly perceived indoor air quality” (Schleibinger et al., 2001a). Exposure to low levels of 4-PCH and other emission products (levels not provided) has been associated with headaches, eye irritation, and nausea (Schachter, 1990; and Van Ert et al., 1987; cited by Beekman et al., 1996).

4-PCH is among new carpet emissions that may be associated with adverse human health effects (Hawkins et al., 1992). The CPSC and the U.S. EPA began a study of carpet emissions in 1989. However, neither agency has established causal link between repeated health effects and new carpets (Hawkins et al., 1992). The CPSC collected complaint reports related to VOCs from new carpet installations from 355 residents in 206 households between 1988 and early 1990 in the United States. The symptoms, which began either immediately or several days of new carpet installation, included upper respiratory tract problems, eye irritation, headaches, rashes, fatigue, difficulty concentrating, headaches, nausea, excessive thirst, dry mouths, burning of eyes, nose and sinuses, incoherent speech, depression, sore throat, itchy skin, burning feet and legs, chronic rhinitis, and lips that were dry, puffy and irritated. There was no control group reported, and relative incidences were not reported (Schachter, 1990; cited by Hodgson et al., 1993; U.S. EPA, 1988). In addition to some of these complaints, unsteady gait was named among U.S. EPA workers in a newly renovated building (Welch and Sokas, 1992).

Studies showed styrene-butadiene formulations caused slight irritation to human skin but no evidence of skin sensitization (Dow Chemical Co., 1990).

9.1.2 Chemical Disposition, Metabolism, and Toxicokinetics of 4-Phenylcyclohexene Metabolites and Analogs

In the absence of metabolism data for 4-PCH, some data are mentioned on some of its metabolites and analogs: 1-phenylcyclohexene (1-PCH), cyclohexene oxide (CHO), and 4-vinylcyclohexene (4-VCH).

The smoke of phencyclidine hydrochloride (PCP) from parsley cigarettes contains 1-PCH as a pyrolysis product (Cook et al., 1982). 1-PCH and its metabolites were found in the plasma and urine of five male volunteers who smoked parsley cigarettes containing 100 µg (0.63 µmol) [³H]PCP. 1-PCH plasma concentrations reached a maximum of 0.35 ± 0.06 pmol/ml (55 pg/ml), and PCP plasma concentrations reached a maximum of 0.62 ± 0.09 pmol/ml. Small amounts of 1-PCH metabolites (0.1 pmol/ml) were found nonconjugated in plasma. Only small amounts

were found in the urine. Larger quantities were located as enzyme-hydrolyzable conjugates in urine. About 0.12 pmol/ml were found as conjugates in plasma.

By analogy with 1-PCH metabolism in microsomal preparations from mouse and rat livers, 4-PCH metabolism might produce cyclohexanones, cyclohexanols, cyclohexenediols, and cyclohexenetriols through hydroxylation and epoxidation-hydrolysis (Cook et al., 1984; Martin et al., 1982.) In rats, metabolites of 1-PCH were 1-phenyl-1-cyclohexen-3-one, 1-phenyl-1-cyclohexen-3-ol, 1-phenyl-6-hydroxy-1-cyclohexen-3-one, 1-phenyl-1-cyclohexene-3,6-diol, *trans*-1-phenyl-1-cyclohexene-3,4-diol, *cis*-1-phenylcyclohexane-1,2-diol, *trans*-1-phenylcyclohexane-1,2-diol, and a substance with the properties of 1-phenylcyclohexane-1,2,3-triol (Cook et al., 1984). 1-PCH metabolism *in vitro* in mouse liver cells produced 1-phenyl-1-cyclohexen-6-ol; 1-phenyl-1-cyclohexen-3-ol; 1-phenyl-1-*O*-6-one; 1-phenylcyclohexane-1,2-diol-mono-trimethylsilyl; 1-phenylcyclohexane-1,2-diol; and a 1-phenylcyclohexane triol (structure unknown) (Martin et al., 1982).

4-PCH might follow the metabolic disposition of 1-PCH, which was studied in rats after intraperitoneal and intravenous administration. The radiolabeled chemical and its metabolites were detected binding irreversibly to tissue proteins (Chakrabarti and Law, 1982; Cook et al., 1983; both cited by Chaturvedi and Kuntz, 1988). After i.v. administration of 0.42 mg/kg (0.0027 mmol/kg) [¹⁴C]1-PCH, its concentration in the blood declined with an elimination half-life of 77 minutes. About 83 percent of the dose was excreted in the urine and feces by 54 hours after administration. In one hour, about 35 percent was excreted in the bile. Less than 6 percent of the [¹⁴C]1-PCH administered was excreted in the urine unchanged; most of the urinary radioactivity was composed of metabolites (Chakrabarti et al., 1983).

1-PCH is biotransformed into reactive metabolites, including generation of 1-PCH epoxides in mice (Martin and Freeman, 1983; Hu et al., 1984; both cited by Chaturvedi and Kuntz, 1988; Martin et al., 1982).

1-PCH in male Swiss-Webster mice induced the hepatic mixed-function oxidase system, which increased the metabolism of PCP, phenobarbital and the contents of cytochrome P-450. It enhanced the metabolism of PCP and inhibited the biotransformation of benzo[*a*]pyrene by aromatic hydrocarbon hydroxylase in a dose-dependent manner (Chaturvedi and Kuntz, 1988).

CHO has been studied for its absorption, distribution, metabolism, and excretion in male Fischer 344 (F-344) rats and female B6C3F₁ mice. After i.v. administration of 50 mg/kg (0.2 mmol/kg) [¹⁴C]CHO, it was distributed, metabolized and excreted rapidly into the urine. Plasma concentrations of CHO rose and fell rapidly and were below the limit of detection within one hour. The average terminal disposition half-life was 19.3 ± 1.6 hours. The apparent volume of distributional steady state was 0.44 ± 0.08 L/kg. The systemic body clearance was 31.3 ± 0.5 ml/kg per minute (Sauer et al., 1997).

After p.o. administration of 10 or 100 mg/kg (0.04 or 0.4 mmol/kg) [¹⁴C]CHO, rats and mice both rapidly excreted the [¹⁴C] equivalents in the urine. At 48 hours, 73 to 93 percent of the dose was recovered in the urine. Between 2 and 5 percent was eliminated in the feces. Unlike its primary metabolite, cyclohexane-1,2-diol, [¹⁴C]CHO was not detected in the blood. That

metabolite and three others were identified in mouse urine: cyclohexane-1,2-diol-*O*-glucuronide; *N*-acetyl-*S*-(2-hydroxycyclohexyl)-*L*-cysteine; and cyclohexane-1,2-diol-*O*-sulfate. Rat urine did not contain the sulfate conjugate (Sauer et al., 1997).

When [¹⁴C]CHO was applied dermally (60 mg/kg [0.2 mmol/kg]) it was absorbed poorly in both rats and mice. About 90 percent of the ¹⁴C was recovered with a charcoal skin trap. Only 4 percent of the dose was absorbed, with urination being the main route of elimination (Sauer et al., 1997).

In rodents, 4-VCH is distributed mainly to adipose tissue. The ethylene carbons are eliminated mainly through urine and exhalation. In mice, rats, and humans, 4-VCH is primarily oxidized in liver microsomes to 4-vinylcyclohexane-1,2-epoxide. Mice and rats metabolize it several times faster than do humans (IARC, 1994b).

In vitro studies of metabolism of 4-VCH by human liver microsomes and *in vitro* studies in rats and mice suggest that ovotoxicity is directly related to the rate at which 4-VCH epoxides are formed. This rate is 13 times higher in mice and twice as high in rats as it is in humans (Smith and Sipes, 1991).

9.1.3 Acute Exposure

Table 1. Acute Toxicity Values for 4-Phenylcyclohexene

| Route | Species (sex and strain) | LD ₅₀ /LC ₅₀ | Reference(s) |
|-------|-----------------------------|--|--|
| Inh. | F-344 rats, male and female | >60 ppm (400 mg/m ³) 6 hr exposure | Nitschke et al. (1991) |
| p.o. | Rats (sex, strain n.p.) | >2 g/kg (0.01 moles) | Van Ert et al. (1987); cited by Nitschke et al. (1991) |

Abbreviations: F-344 = Fischer 344; hrs = hours; Inh. = inhalation; n.p. = not provided; p.o. = *per os* (oral)

Swiss-Webster mice suffered severe toxicity and mortality when exposed to less than 1 ppm (6 mg/m³) 4-PCH vapor (details not provided) (Anderson, 1992; Pesticide and Toxic Chemical News, 1992; both cited by Beekman et al., 1996). But Beekman and Johnson (1992; cited by Beekman et al., 1996) found that Swiss-Webster mice suffered no treatment-related effects from whole-body exposure to 44 ppm (280 mg/m³) 4-PCH for six hours. In another study, Swiss-Webster mice exposed to 50 ppm 4-PCH for six hours (44 ppm time-weighted average) also showed no treatment-related effects (SBLMC, 1992).

Male and female F-344 rats (five/sex/dose), 7-weeks old, underwent whole-body exposure (98 percent pure) to 16 ppm or 60 ppm (104 mg/m³ or 400 mg/m³) 4-PCH for six hours. There was no control group. Airflow was about 30 liters per minute. Clinically visible changes seen in the animals exposed to the lower dose were not deemed exposure related. No clinically visible effects were seen in the animals exposed to the higher dose during exposure or during the 2-week post-exposure period. Body weights in both groups increased normally, and the necropsy revealed no exposure-related effects (Dow Chemical Co., 1989b; Nitschke et al., 1991). A preliminary report stated carpet emissions caused adverse pulmonary and nervous system responses similar to those caused by 0.2 ppm 4-PCH (National Federation of Federal Employees,

1992). Studies investigating the toxic effects of volatile emissions from carpets heated to 37°C have been conducted in mice (SBLMC, 1992), although in these studies, the actual compounds emitted were not determined. Neither did the studies include the composition of the carpet fiber and backing. These studies investigated sensory and pulmonary irritation, neurotoxicity, and death. Five different carpet samples were investigated. The animals underwent two hours of exposure per day, with a rest period in between, for two days. One of the samples induced overt neurotoxicity and death. When the backing and glue from this particular carpet were evaluated independently, sensory and pulmonary irritation occurred, although these effects decreased with time, and no neurotoxicity was found. Slight sensory and pulmonary irritation was found with the other carpet samples (SBLMC, 1992).

Commercial styrene-butadiene formulations associated with 4-PCH displayed low toxicity. In a study of rats, one in a sample of five died after receiving 10 g/kg p.o. of a styrene-butadiene formulation. At the highest oral dose tested, (3.98 g/kg), one formulation induced weight loss and moderate kidney damage (Dow Chemical Co., 1990).

9.1.4 Short-term and Subchronic Exposure

The details of studies by Beekman et al. (1996), Dow Chemical Co. (1989b; Nitschke et al., 1991) and SBLMC (1993; Beekman et al., 1996) are in **Table 2**.

9.1.5 Chronic Exposure

No chronic exposure studies of 4-PCH were located.

9.1.6 Synergistic/Antagonistic Effects

No synergistic/antagonistic effect studies of 4-PCH were located.

9.1.7 Cytotoxicity

A commercial styrene-butadiene formulation was tested on cultured mouse fibroblast cells and was shown to be noncytotoxic (SBLMC, 1990b).

9.2 Reproductive and Teratological Effects

Female B6C3F₁ mice (28 days old, 15 per dose group) were administered 3.0 or 6.0 mmol/kg (475 or 950 mg/kg) 4-PCH (98% pure) intraperitoneally (i.p.), once a day for 30 days. The negative control group was dosed with sesame seed oil. Animals were sacrificed on first day of diestrus after the last dose. Neither dose of 4-PCH had any effect on follicle numbers compared to those of the sesame oil control group. Light microscopic examination of 4-PCH-treated ovaries failed to detect any histologic changes. The number of estrous cycles in 30 days decreased from 4.8 in the control group to 3.2 in the higher 4-PCH-dose group. The number of estrous cycles returned to control values within 30 days of treatment discontinuation (Hooser et al., 1993).

Table 2: Short-term and Subchronic Exposure to 4-Phenylcyclohexene

| Species, Strain, and Age, Number, and Sex of Animals | Chemical Form and Purity | Route, Dose, Duration, and Observation Period | Results/Comments | Reference |
|---|--------------------------|--|---|--|
| Mouse, Swiss-Webster, 5-wk old, 20 M/concentration | 4-PCH, 97.2% pure | Inh: (whole-body exposure) 0 or 62 ppm (0 or 401 mg/m ³), 6 hr/d, 9 consecutive d followed by in-life observations and neurohistopathology on selected tissues. | No treatment-related CNS lesions were found. | Beekman et al. (1996); SBLMC (1993) |
| Mouse, Swiss-Webster, 5-wk old, M and F, 20/sex/concentration | 4-PCH, 97.2% pure | Inh: (whole-body exposure) 0, 7, 18, or 71 ppm (0, 50, 120, 460 mg/m ³), 6 hr/d, 9 consecutive d. 50% animals underwent in-life observations; 50% underwent neurological evaluations. Neurohistopathology conducted on 5 mice/sex/dose. | No clear treatment-related effects were noted despite exposure at near-saturated atmosphere. No effects could be definitively related to 4-PCH based on in-life parameters, FOB, motor activity, or gross pathological or histopathological examination of organs and tissues. | |
| Rat, F-344, 6- to 8-wk old, M and F, 10/sex/concentration | 4-PCH, 98% pure | Inh: (whole body exposure) 0, 1, 10, or 50 ppm (0, 7, 70, or 300 mg/m ³) over 2 wk for 6 hr/d, 5 d/wk, for 9 exposures. Animals were observed each day, and body weights were recorded periodically. All animals sacrificed 1 d after the last exposure. | The TWA mean daily analytical concentrations were 1.2, 10.0, and 49.8 ppm. No treatment-related clinical signs were observed. All rats survived until the necropsy. Hematologic parameters were not altered following exposures to 4-PCH. Urinalysis revealed a statistically significant decrease in the specific gravity (1.030 ± 0.011) for F exposed to 50 ppm relative to the control group (1.043±0.015); authors concluded that this was of no toxicologic significance as it was within the range of historical control values. The statistically significant increase in mean relative brain weight for M exposed to 50 ppm was thought to be a reflection of the non-significant reduction in terminal fasted body weight. No treatment-related gross or microscopic changes were observed. | Dow Chemical Co. (1989b); Nitschke et al. (1991) |

Abbreviations: CNS = central nervous system; d = day(s); F = female; F-344 = Fischer 344; FOB = functional observational battery; hr = hour(s); Inh = inhalation; M = male; 4-PCH = 4-phenylcyclohexene; TWA = time weighted average; wk = week(s)

9.3 Carcinogenicity

No carcinogenicity studies of 4-PCH were located.

9.4 Initiation/Promotion Studies

No initiation-promotion studies of 4-PCH were located.

9.5 Anticarcinogenicity

No anticarcinogenicity studies of 4-PCH were located.

9.6 Genotoxicity

No genotoxicity studies of 4-PCH were located.

9.7 Cogenotoxicity

No cogenotoxicity studies of 4-PCH were located.

9.8 Antigenotoxicity

No antigenotoxicity studies of 4-PCH were located.

9.9 Immunotoxicity

Dermal sensitization to 4-PCH was studied in Hartley albino guinea pigs. Material was applied dermally to 10 male guinea pigs once a week for three weeks. The test material was placed in a naïve area of the animals 14 days after the final induction application. DER331 epoxy resin in DPGME was applied to one group as a positive control. Twenty-four and 48 hours later, they were graded on induction response. The non-irritating concentration of 4-PCH used for induction was 10 percent. The same concentration was applied for the challenge phase. The challenge application caused no response (Dow Chemical Co., 1989a; Dow Chemical Co., 1989b; Nitschke et al., 1991).

Toxicity studies of commercial styrene-butadiene formulations containing 4-PCH showed it caused slight skin irritation and swelling in rabbits, guinea pigs and rats, with no evidence of permanent skin damage or of skin sensitization (Dow Chemical Co., 1990; SBLMC, 1990b).

9.10 Other Data

The 1996 CPSC study tested 17 compounds associated with carpet and carpet cushion emissions. Sensory irritation in mice was determined by measuring a concentration-dependent decrease in respiration rate. Sensory irritation for each compound was compared based on the levels predicted to cause 50 percent, 20 percent, and 12 percent respiratory depression, or RD₅₀, RD₂₀ and RD₁₂, measured by the American Society for Testing and Materials bioassay designation E (ASTM E) (ASTM, 1984; cited by CPSC, 1996). Pulmonary irritation was determined by measuring a post-expiratory bradypnea. The average respiratory frequency was based on percentage of baseline frequency (CPSC, 1996).

Mice were exposed to vapors, generated using J-tube methodology. They were exposed to one chemical at a time, head only, for 60 minutes. Of nine exposures, the lowest, 23 mg/m³ did not significantly depress respiration. The 4-PCH RD₅₀ was 319 mg/m³ (49 ppm), the RD₂₀ was 59.6, and the RD₁₂ was 38.1 (CPSC, 1996). Respiratory depression and onset of sensory irritation were relatively rapid. At all exposures to 4-PCH, except at the lowest concentrations, there was mild recovery toward baseline during the exposure period. After exposure, there was recovery toward baseline for all exposures (CPSC, 1996).

Out of 11 chemicals tested for irritation response, 4-PCH was the least irritating, with an RD₂₀ of 9.2 ppm (59.6 mg/m³). The most irritating of the chemicals was 2-methylnaphthalene with an RD₂₀ of 0.4 ppm (2.5 mg/m³). Installation of 4-PCH in surgically exposed tracheas of rats yielded pulmonary effects. This result is not indicative of inhalation exposure to 4-PCH (Van Ert et al., 1987; cited by Beekman et al., 1996).

Commercial styrene-butadiene formulations that contain 4-PCH caused temporary corneal injury or irritation in rabbits but caused no permanent damage (SBLMC, 1992; Dow Chemical Co., 1990).

10.0 Structure-Activity Relationships

It is possible that 4-PCH is a moderate sensory or respiratory irritant based on similarities of structures and activities of known irritants (Nielsen and Alarie, 1982; Nielsen et al., 1984; both cited by Hodgson et al., 1993).

This section does not include complex 4-PCH analogs such as morphine [57-27-2] and related compounds (\pm)-tilidine [20380-58-9] and Δ^8 -tetrahydrocannabinol [5957-75-5] and derivatives. It also does not include simpler cyclohexenes, which are monoterpenes, and simple derivatives such as *D*-limonene [5989-27-5] and α -terpineol [98-55-5] (ChemID Plus, 2002; Budavari, 1996).

A few cyclohexenylcyclohexenes (bicyclohexenyls) were identified, but no biomedical database records were identified for them, and none of the compounds is listed in the TSCA Inventory. These included 3,3-bicyclohexenyl [CAS No. 1541-20-4] with 57 CAPLUS records as of April 1, 2002; 3-(2-cyclohexenyl) cyclohexene [CAS No. 65182-00-2] with only one CAPLUS record; and 1-(1-cyclohexenyl) cyclohexene, also called 2,2-bicyclohexene [CAS No. 1128-65-0] with 80 CAPLUS records.

Selected toxicity information for cyclohexene, 1-PCH, CHO, 4-VCH, and biphenyl are discussed here.

Cyclohexene is converted to *trans*-cyclohexenediol in liver microsomes from male Holzman rats and in New Zealand white rabbits, with an intermediate epoxide (Leibman and Ortiz, 1970). It was not mutagenic in *S. typhimurium* (strains and doses n.p.; metabolic activation not mentioned) (Sycheva et al., 2000).

1-PCH is a pyrolysis product of phencyclidine, or PCP, a psychotomimetic drug of abuse taken by smoking (Chaturvedi and Kuntz, 1988).

Acute Exposure

The LD₅₀s for PCP in male CD-1 mice, according to route of administration, were 57 μ mol/kg i.v., 230 μ mol/kg i.p., and 284 μ mol/kg. The LD₅₀s for PCP in female CD-1 mice, according to route of administration, were 76 μ mol/kg i.v., 292 μ mol/kg i.p., and 342 μ mol/kg p.o. The LD₅₀s for 1-PCH in male CD-1 mice, according to route of administration, were 448 μ mol/kg (70.89 mg/kg) i.v., 1,580 μ mol/kg (250.02 mg/kg) i.p., and >9,500 μ mol/kg (>1,500 mg/kg) p.o. The LD₅₀s for 1-PCH in female CD-1 mice, according to route of administration, were 425 μ mol/kg i.v., 1,570 μ mol/kg i.p., and >9,500 μ mol/kg p.o. (Holsapple et al., 1982).

Subacute Exposure

CD-1 mice underwent a 14-day exposure (i.p.) to PCP at 41 μ mol/kg and 124 μ mol/kg. Another group of mice underwent a 14-day exposure to 1-PCH at 63.4, 317, and 634.5 μ mol/kg (10,032, 50, 160, and 100,403.3 μ g/kg). PCP significantly increased kidney weight (Holsapple et al. 1982). The average body weight and thymus weight decreased significantly in females receiving the highest dose of 1-PCH, and in males, this dose was associated with significantly decreased body, thymus, liver, and spleen weights (Holsapple et al., 1982).

Short-Term and Subchronic Exposure

The subchronic effects of PCP and 1-PCH on mice were compared. Impaired motor function was measured to compare the acute behavioral effects of PCP and 1-PCH, using the inverted screen test. In male mice, ICR outbred albino weanlings, 50 percent of the effective dose (ED₅₀) for each compound was determined for inhibition and completion of each task. Immediately after injection, the molar ED₅₀ for 1-PCH was 325 μ mol/kg (16.2 g/kg), 79 times the ED₅₀ for PCP. After five minutes, the effects of 1-PCH were no longer evident (Holsapple et al., 1982).

CHO is a monomer intermediate used to synthesize pesticides, pharmaceuticals, and perfumes. When administered i.v. and p.o. to rats and mice, CHO was rapidly eliminated and excreted into the urine. It was postulated that this compound is unlikely to cause toxicity in the whole animal because of its rapid elimination. Rats and mice were given CHO p.o. and dermally for 28 days in order to evaluate its toxicity (Sauer et al., 1997).

Subacute Exposure

Changes in final body weights or relative organ weights were not statistically significant in rats or mice treated with CHO (up to 100 mg/kg p.o. [0.4 mmol/kg] or up to 60 mg/kg [0.2 mmol/kg] topically). Necropsy did not reveal compound-related lesions (Sauer et al., 1997).

Genotoxicity

CHO was mutagenic at 5 to 20 mmol/L (1,000 mg/kg to 5,000 mg/kg) in *Klebsiella pneumoniae*. No metabolic activation was used (Voogd et al., 1981). CHO did not cause micronuclei to form, and it was not mutagenic in *Salmonella* (strains and presence of metabolic activation not provided) (NTP, 2002).

4-VCH, also called 4-ethenylcyclohexene, is an industrial byproduct of rubber production that is known to cause ovarian damage and cancer in animals (Collins and Manus, 1987; Dobson and Fenton, 1983; both cited by Hooser et al., 1993). Rubber curers are exposed to this chemical (Collins and Manus, 1987; cited by Hooser et al., 1993).

Human Data

4-VCH and its diepoxide are possibly carcinogenic to humans (IARC, 1994a; IARC, 1994b).

Acute Exposure

In four acute toxicity studies in mice, the LD₅₀ of inhaled 4-VCH was 27 g/m³ (6.1 parts per thousand); in rats, it was 8,000 ppm (40,000 mg/m³) after four hours (RTECS GW665000, 2000).

Chronic Exposure

In a study of 13-week exposure to 4-VCH via gavage, final body weights in male F-344 rats were reduced at a dose of ≥400 mg/kg (4 mmol/kg) 4-VCH. In female F-344 rats, final body weights were reduced at a dose of 800 mg/kg (7 mmol/kg). A dose of 600 mg/kg (6 mmol/kg) reduced body weight in female B6C3F₁ mice (NTP TR-303, 1986).

In male F-344 rats given 1,250 mg/kg (12 mmol/kg) 4-VCH in 13-week studies, there was hyaline droplet degeneration of the proximal convoluted tubules in the kidney in a dose-related fashion. In female B6C3F₁ mice receiving 1,200 mg/kg (11 mmol/kg), the number of primary follicles and mature graafian follicles were reduced (NTP TR-303, 1986).

Reproductive Effects

In one study, CD-1 mice were administered 4-VCH (0 to 500 mg/kg [5 mmol/kg]) by gavage. Exposure for 14 weeks did not affect fertility, mean number of litters per pair, or live litter size, the proportion of pups born alive, or adjusted live pup weight. At the high dose, absolute live pup weight and female body weight decreased. 4-VCH did not affect preweaning growth or pup survival. The highest dose had no significant effect on reproductive competence in either generation F₀ or F₁. However, in F₁, there were significant reductions in spermatid head count and ovarian follicles (NTP, 1991).

Female, 28-day-old B6C3F₁ mice were treated i.p. with 6.0 mmol/kg (650 mg/kg) 4-VCH twice, seven days apart. The animals were killed on the first day of diestrus after the last dose. When ovaries were examined, the numbers of small and growing follicles were reduced dramatically in animals dosed with 6 mmol/kg (650 mg/kg) 4-VCH when compared to those dosed with 6 mmol/kg (900 mg/kg) 4-PCH daily for six days. Because only the oocytes within the follicles were destroyed, researchers postulated that 4-VCH interacts with a cellular component necessary to oocyte survival (Hooser et al., 1993). The researchers postulate that the presence of the 4-phenyl group might prevent 4-PCH from interacting with a receptor or enzyme.

After a 30-day i.p. administration of 4-VCH to mice, ovarian follicles were significantly depleted. No change in ovarian follicle numbers was observed after treatment with 4-VCH structural analogs vinylcyclohexane, ethylcyclohexene, and cyclohexene. Unlike 4-VCH, each contains only one unsaturated carbon bond. Neither were the mono-epoxide forms of the analogs ovotoxic (doses n.p. in abstract) (Doerr et al., 1995). 4-VCH, when administered as a single 400 mg/kg (4 mmol/kg) dose p.o. to female rats and mice, was not retained in the ovaries of either species. In mice, the levels of VCH-1,2-epoxide in the blood were much higher than in rats (Smith et al., 1990a). In another study, 4-VCH caused a smaller percent oocyte loss than did its epoxides in both mice and rats. The ED₅₀ dose was defined as that which reduced the small oocyte count to 50 percent of that of controls. 4-VCH had a 2.7 mmol/kg (290 mg/kg) ED₅₀ in

mice and caused no detectable oocyte loss at the highest dose, 7.4 mmol/kg (800 mg/kg) in rats. 4-VCH diepoxide was especially potent, with an 0.2 mmol/kg ED₅₀ in mice and an 0.4 mmol/kg ED₅₀ in rats (Smith et al., 1990b).

Carcinogenicity

4-VCH, administered by gastric intubation to female mice, produced granulose-cell tumors, mixed ovary tumors, and adrenal subcapsular tumors. In male mice, the incidence of lymphoma and of lung tumors increased. Gastric intubation of 4-VCH in rats increased incidences of squamous-cell tumors on male's skin and on the clitoral glands in females. In its evaluation, the IARC considered 4-VCH *possibly carcinogenic to humans (Group 2B)* (IARC, 1994a).

In groups of female B6C3F₁ mice dosed with 4-VCH by gavage for two years, the incidence of uncommon ovarian neoplasms increased significantly ($P < 0.01$), as did the incidence of tumors and carcinomas in granulosa cells. There was also a slight increase in adrenal gland adenomas in high-dose females (NTP TR-303, 1986).

Genotoxicity

4-VCH was not mutagenic to *Salmonella typhimurium* strains TA100, TA1535, TA1537 or TA98, with or without metabolic activation. The monoepoxide metabolites of 4-VCH were not mutagenic to *S. typhimurium* either (strains and concentrations n.p.). But 4-vinylcyclohexene diepoxide and other metabolites have demonstrated mutagenicity in *Salmonella* and/or induced chromosomal damage *in vitro*. For instance, 4-vinyl-1,2-epoxycyclohexane induced micronuclei formation in cultured Chinese hamster cells (concentrations n.p.) (NTP TR-303, 1986; IARC, 1994a).

Other Data

During a chamber study of carpet emissions, the concentration of 4-VCH, 0.07 ppb (0.3 µg/m³), dropped to nondetectable levels when 409 ppb ozone was added. Levels of 4-PCH emissions also dropped in the presence of ozone (Weschler et al., 1992).

Biphenyl is used in the agricultural and chemical industries as a fungicide, bactericide, and wood preservative (ChemID Plus 000092524, undated). It was an intermediate in the production of polychlorinated biphenyls (PCBs) until the early 1970s. It occurs in coal tar, crude oil, and natural gas (IPCS/WHO, 1999).

Human Studies

In one report of human exposure, a single skin application of 0.5 ml 4 percent biphenyl solution to two subjects caused no apparent irritation. Nor did 23 percent biphenyl in oil applied to skin three times a week for eight weeks. A volunteer given 35 mg biphenyl p.o. (0.23 mmol) suffered no adverse effects. Among workers exposed to biphenyl vapors and other substances, cases of headache, nausea, and respiratory tract inflammation were found. In a case study of workers, long-term exposure to high concentrations of biphenyl was associated with human liver damage and effects on the central and peripheral nervous systems. A woman who had worked with biphenyl-impregnated paper for 25 years suffered chronic and persistent hepatitis attributed to the biphenyl absorption through the skin and digestive tract (Macintosh, 1945; Selle, 1952;

Farkas, 1939; Weil et al., 1965; Haekkinen et al., 1973; Carella and Bettolo, 1994; all cited by IPCS/WHO, 1999).

Acute Exposure

The LD₅₀ in rats and mice administered biphenyl p.o. was 1,900 mg/kg (12 mmol/kg) body weight. In mice dosed by inhalation for four hours, the LC₅₀ was >43 ppm (275 mg/m³) (BUA, 1990; Sun Co. Inc., 1977a; both cited by IPCS/WHO, 1999).

Short-Term and Subchronic Exposure

Male and female Wistar rats were fed 0 to 450 mg/kg biphenyl (2.9 mmol/kg) per day for 21 days. At doses of 50 and 150 mg/kg (0.30 and 0.97 mmol/kg), there were increased relative kidney weights and polycystic renal changes, including increased urine volume and specific gravity. At doses of 500 or 1,000 mg/kg biphenyl (3 to 6 mmol/kg) in the diet for 14 days, an increase in urine volume and other kidney changes were observed (Sondergaard and Blom, 1979; cited by IPCS/WHO, 1999).

Chronic Exposure

Rabbits, rats, and mice were exposed to biphenyl dust by inhalation for up to 13 weeks. Rabbits exhibited no adverse effects. Rats exhibited increased mortality and irritated mucous membranes after exposure to 40 or 300 mg/m³ (6 to 50 ppm) biphenyl. At an exposure of 5 mg/m³ (0.8 ppm), the mortality of mice increased slightly. All mice showed irritation of the upper respiratory tract. Necropsies of rats and mice showed inflammatory bronchopulmonary changes. No information was provided on controls (Deichmann et al, 1947; cited by IPCS/WHO, 1999; Anonymous, 2000).

In rats fed diets containing 0 to 4,500 mg/kg biphenyl (0 to 29 mmol/kg) for two years, there was a lowest-observed-effect level of 38 mg/kg (0.25 mmol/kg) per day, based on changes in hematological parameters (Anonymous, 2000).

In a study in which male and female Wistar rats were administered biphenyl in the range of 0 to 20,000 mg/kg (estimated daily intake, 0 to 1,500 mg/kg [9.7 mmol/kg]) for ten weeks, there was a dose-dependent reduction in weight gain and increased serum activities of some enzymes (Takita, 1983; cited by IPCS/WHO, 1999).

Several 24-week rat studies were located, in which 0 or 5,000 mg/kg biphenyl was administered in the diet. At the 5,000 mg/kg dose, reduced body weight gain was noted, as were increased kidney weights. Increased incidences of stones in the urinary tract and histopathological changes in the kidney were observed. One source noted the onset of kidney-damaging effects at 30 days for 188 mg/kg (1.22 mmol/kg) daily estimated intake (2,500 mg/kg total intake) and 375 mg/kg (2.43 mmol/kg) daily estimated intake (5,000 mg/kg total intake) (Tamano et al., 1993; Shibata et al., 1989; Booth et al., 1961; Kurata et al., 1986; Shiraiwa et al., 1989; all cited by IPCS/WHO, 1999).

In male and female CD-1 mice exposed to 25 or 50 ppm (160 or 320 mg/m³) biphenyl for seven hours per day, five days per week, for 13 weeks, there were no effects that could be attributed to biphenyl (Sun Co., Inc., 1977b; cited by IPCS/WHO, 1999).

Male and female Crj:BDF₁ mice fed 0 to 6,000 mg/kg biphenyl (0 to 900 mg/kg [0 to 6 mmol/kg] per day) for 104 weeks experienced degenerative changes in the respiratory epithelium of the nasal cavity and nasopharynx and blood chemistry. There were also degenerative changes in the kidneys (Japan Bioassay Research Center, 1996; cited by IPCS/WHO, 1999).

Carcinogenicity

Wistar rats given 0 to 5,000 mg/kg biphenyl p.o. (0 to 375 mg/kg [0 to 2.43 mmol/kg] per day) for 75 weeks experienced no increased incidence of tumors (Takita, 1983; Shiraiwa et al., 1989; both cited by IPCS/WHO, 1999). In male F-344/DuCrj rats, those that received biphenyl in the diet at 4,500 mg/kg (29 mmol/kg) for 104 weeks experienced a significant increase in neoplastic and nonneoplastic lesions of the urinary bladder. There was dose-dependent increase in hyperplasia of renal pelvis epithelium in male and female rats. Hematological effects were noted (Japan Bioassay Research Center, 1996; cited by IPCS/WHO, 1999).

Male and female Crj:BDF₁ mice fed 0 to 6,000 mg/kg biphenyl (0 to 900 mg/kg [0 to 6 mmol/kg] per day) for 104 weeks experienced a slight increase in liver tumors. In the females, there were basophilic cell foci of the liver (Japan Bioassay Research Center, 1996; cited by IPCS/WHO, 1999).

Reproductive and Teratological Effects

Female Wistar rats were administered 0 to 1,000 mg/kg (65 μ mol/kg) biphenyl by gavage on days 6 through 15 of gestation. Maternal toxicity was observed in the highest dose group, where five of 20 died. Litter size was not affected in a study in which male and female rats were administered diets containing 75 and 375 mg/kg biphenyl (0.49 and 2.43 mmol/kg respectively), per day before mating and during gestation. Male and female rats and mice administered 500 to 4,500 mg/kg biphenyl (3 to 29 mmol/kg) p.o. for two years did not undergo histopathological changes to their reproductive systems (Khera et al., 1979; Ambrose et al., 1960; Japan Bioassay Research Center, 1996; all cited by IPCS/WHO, 1999).

Initiation/Promotion Studies

B6C3F₁ male mice, administered water with 0.05 percent *N*-butyl-*N*-hydroxybutylnitrosamine (BBN) for four weeks followed by a diet containing 1,500 mg/kg biphenyl (9.7 mmol/kg) per day for 32 weeks showed a reduction in body weight and in average food consumption and an increase in urinary bladder weight. Biphenyl caused interstitial nephritis in the kidneys with and without BBN-pretreatment (Tamano et al., 1993; cited by IPCS/WHO, 1999).

Albino mice that were exposed once dermally to 9,10-dimethyl-1,2-benzanthracene, then received dermal applications of 20 percent biphenyl in benzene twice weekly for 15 weeks did not exhibit skin papillomas or carcinomas, and neither did biphenyl-only controls (Boutwell and Bosch, 1959; cited by IPCS/WHO, 1999).

Male Wistar rats that were administered 0.1 percent *N*-ethyl-*N*-hydroxyethylnitrosamine for two weeks as an initiator, followed by administration of 1 to 0.5 percent biphenyl for 34 weeks, had no increase in dysplastic foci and renal cell tumors that were induced by the initiator. Rats administered biphenyl showed an increase in stones of the kidneys, ureter, and bladder with or without *N*-ethyl-*N*-hydroxyethylnitrosamine (Shiraiwa et al., 1989; cited by IPCS/WHO, 1999).

Male F-344 rats were administered drinking water with 0.05 percent BBN as an initiator for four weeks, followed by 375 mg/kg (2.43 mmol/kg) per day biphenyl in the diet for 32 weeks. Histopathological findings showed more incidences of hyperplasia, papilloma, and carcinoma of the urinary bladder with both biphenyl and the initiator than without the initiator (Kurata et al., 1986; cited by IPCS/WHO, 1999).

Genotoxicity

Biphenyl did not cause unscheduled DNA synthesis (concentrations n.p.) in human lung fibroblasts WI-38, with and without metabolic activation (Waters et al., 1982; cited by IPCS/WHO, 1999). It also did not cause DNA damage at a concentration of 15.4 $\mu\text{g/ml}$ (0.0999 $\mu\text{mol/ml}$) in human fibroblasts without metabolic activation in the “nick translation assay.” Metabolic activation was not used (Snyder and Matheson, 1985; cited by IPCS/WHO, 1999).

Biphenyl caused unscheduled DNA synthesis at concentrations of 0.002 to 154 $\mu\text{g/ml}$ (0.01 to 10 mmol/ml) in rat hepatocytes with metabolic activation (Williams, 1978; Brouns et al., 1979; Probst et al., 1981; all cited by IPCS/WHO, 1999).

Male Sprague-Dawley rats were exposed by inhalation to 64 or 320 mg/m^3 biphenyl (10 to 50.1 ppm) as a dust aerosol for seven hours per day, five days per week for 20 exposures in 30 days. The frequency of chromosomal aberrations in bone marrow did not increase (Dow Chemical Co., 1976; cited by IPCS/WHO, 1999).

Biphenyl was not mutagenic at concentrations of 0 to 5,000 μg (30 μmol) per plate in *S. typhimurium* strains TA92, TA94, TA97a, TA98, TA100, TA102, TA1532, TA1535, TA1537, TA1538, and TA2636, with or without metabolic activation (Cline and McMahon, 1977; Purchase et al., 1978; Kawachi et al., 1980; NTP, 1980; Bronzetti et al., 1981; Probst et al., 1981; Waters et al., 1982; Glatt et al., 1992; 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; all cited by IPCS/WHO, 1999).

Biphenyl was tested in several strains of *Escherichia coli*. It was not mutagenic at concentrations of 0.1 to 1,000 $\mu\text{g/ml}$ (0.0006 to 65 $\mu\text{mol/ml}$) in *E. coli* strains WP2 and WP2 uvrA, with and without metabolic activation (Cline and McMahon, 1977; Waters et al., 1982; cited by IPCS/WHO, 1999). Biphenyl did not cause DNA damage at concentrations of 2.4 to 154 $\mu\text{g/ml}$ (0.016 to 1 $\mu\text{mol/ml}$) in *E. coli* strain PQ37 with or without metabolic activation (Brams et al., 1987; cited by IPCS/WHO, 1999).

Biphenyl was not mutagenic (concentrations n.p.) in *Bacillus subtilis* when using the rec assay. No metabolic activation was cited (Kawachi et al., 1980; cited by IPCS/WHO, 1999).

Biphenyl was tested in two strains of *Saccharomyces*. At concentrations of $\leq 154 \mu\text{g/ml}$ (1 $\mu\text{mol/ml}$), biphenyl was mutagenic and caused gene conversion in *S. cerevisiae* D7, with and without metabolic activation (Pagano et al., 1983; cited by IPCS/WHO, 1999). Biphenyl (concentrations n.p.) did not cause gene conversion in *S. cerevisiae* D3 with and without metabolic activation (Waters et al., 1982; cited by IPCS/WHO, 1999).

Biphenyl was mutagenic at concentrations of 0 to 61 $\mu\text{g/ml}$ (0 to 0.406 $\mu\text{mol/ml}$) in L5178Y TK \pm cells in a mouse lymphoma assay with, but not without, metabolic activation (Wangenheim and Bolcsfoldi, 1988; cited by IPCS/WHO, 1999).

Biphenyl was mutagenic at 231 $\mu\text{g/ml}$ (1.509 $\mu\text{mol/ml}$) in mouse L5178Y cells using the alkaline unwinding assay with, but not without, metabolic activation (Garberg et al., 1988; cited by IPCS/WHO, 1999).

Biphenyl was tested on several strains of Chinese hamster lung cell lines (V79, CHL, and DON). Biphenyl *in vitro* caused chromosomal aberrations and sister chromatid exchanges. It was mutagenic at 100 $\mu\text{g/ml}$ (7 $\mu\text{mol/ml}$) in V79 cells with, but not without, metabolic activation (Glatt et al., 1992; cited by IPCS/WHO, 1999). Biphenyl caused chromosomal aberrations at 20 $\mu\text{g/ml}$ (0.1 $\mu\text{mol/ml}$) in CHL cells with metabolic activation. Without metabolic activation, biphenyl did not cause gene mutations in CHL cells at 125 $\mu\text{g/ml}$ (0.811 $\mu\text{mol/ml}$) (Ishidate and Odashima, 1977; Kawachi et al., 1980; Sofuni et al., 1985; all cited by IPCS/WHO, 1999). Biphenyl caused chromosomal aberrations and sister chromatid exchanges at concentrations of 15.4 to 154 $\mu\text{g/ml}$ (0.1 to 1 $\mu\text{mol/ml}$) in DON cells (Abe and Sasaki, 1977; cited by IPCS/WHO, 1999). Biphenyl (concentrations n.p.) did not cause sister chromatid exchange in CHL cells. No metabolic activation was used (Kawachi et al., 1980; cited by IPCS/WHO, 1999).

Immunotoxicity

Repeated dermal application of 0.5 g/kg biphenyl (0.003 mol/kg) for two hours a day, five days a week, decreased body weight in rabbits. There was no effect on skin observed in these studies. Another study revealed no adverse effects when 600 or 2,000 mg/kg (4 mmol/kg or 10 mmol/kg) biphenyl was applied eight hours per day, five days per week, to intact and abraded skin of rabbits (Deichmann, et al., 1947; Newell, 1953; both cited by IPCS/WHO, 1999; Anonymous, 2000).

Biphenyl was nonirritating and nonsensitizing to intact and scarified rabbit and guinea pig skins (BUA, 1990; Dreist and Kolb, 1993; both cited by IPCS/WHO, 1999).

11.0 Online Databases and Secondary References

11.2 Online Databases

Chemical Information System Files

SANSS (Structure and Nomenclature Search System)

TSCATS (Toxic Substances Control Act Test Submissions)

DIALOG Files

DI GENES (Chemical Economics Handbook)

National Library of Medicine Databases

EMIC and EMICBACK (Environmental Mutagen Information Center)

STN International Files

| | | | |
|-----------|---------|----------|-----------|
| AGRICOLA | CAPLUS | NIOSHTIC | TOXLINE |
| BIOSIS | EMBASE | NTIS | BIOTECHNO |
| CA | HSDB | PROMT | |
| CABA | LIFESCI | Registry | |
| CANCERLIT | MEDLINE | RTECS | |

TOXLINE includes the following subfiles:

| | |
|---|--------|
| Toxicity Bibliography | TOXBIB |
| International Labor Office | CIS |
| Hazardous Materials Technical Center | HMTC |
| Environmental Mutagen Information Center File | EMIC |
| Environmental Teratology Information Center File (continued after 1989 by DART) | ETIC |
| Toxicology Document and Data Depository | NTIS |
| Toxicological Research Projects | CRISP |
| NIOSHTIC [®] | NIOSH |
| Pesticides Abstracts | PESTAB |
| Poisonous Plants Bibliography | PPBIB |
| Aneuploidy | ANEUPL |
| Epidemiology Information System | EPIDEM |
| Toxic Substances Control Act Test Submissions | TSCATS |
| Toxicological Aspects of Environmental Health | BIOSIS |
| International Pharmaceutical Abstracts | IPA |
| Federal Research in Progress | FEDRIP |
| Developmental and Reproductive Toxicology | DART |

In-House Databases

CPI Electronic Publishing Federal Databases on CD

Current Contents on Diskette[®]

The Merck Index, 1996, on CD-ROM

Other Databases

TOXCENTER

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Appendix: Units and Abbreviations

°C = degrees Celsius

µg/L = microgram(s) per liter

µg/m³ = microgram(s) per cubic meter

µg/mL = microgram(s) per milliliter

µM = micromolar

ACGIH = American Conference of Governmental Industrial Hygienists

bw = body weight

CNS = central nervous system

EPA = Environmental Protection Agency

F = female(s)

g = gram(s)

g/mL = gram(s) per milliliter

h = hour(s)

HD = high dose

HSDB = Hazardous Substances Data Bank

i.p. = intraperitoneal(ly)

kg = kilogram(s)

L = liter(s)

lb = pound(s)

LC = liquid chromatography

LC₅₀ = lethal concentration for 50% of test animals

LD₅₀ = lethal dose for 50% of test animals

LD = low dose

LOD = limit of detection

M = male(s)

MD = mid dose

mg/kg = milligram(s) per kilogram

mg/m³ = milligram(s) per cubic meter

mg/mL = milligram(s) per milliliter

min = minute(s)

mL/kg = milliliter(s) per kilogram

mm = millimeter(s)

mM = millimolar

mmol = millimole(s)

mmol/kg = millimoles per kilogram

mo = month(s)

mol = mole(s)

mol. wt. = molecular weight

NIEHS = National Institute of Environmental Health Sciences

NIOSH = National Institute for Occupational Safety and Health

NOEL = no observable effect level

nm = nanometer(s)

n.p. = not provided

OSHA = Occupational Safety and Health Administration

PEL = permissible exposure limit

ppb = parts per billion

ppm = parts per million

p.o. = peroral(ly), *per os*

REL = relative exposure limit

s = second(s)

s.c. = subcutaneous(ly)

STEL = short-term exposure limit

TSCA = Toxic Substances Control Act

TWA = time-weighted average

USEPA = U.S. Environmental Protection Agency

wk = week(s)

yr = year(s)