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Environmental Protection Agency

of Emergency and Remedial Response
Washington DC 20460

Office of Research and Development
Office of Health and Environmental Assessment
Environmental Criteria and Assessment Office
Cincinnati OH 45268

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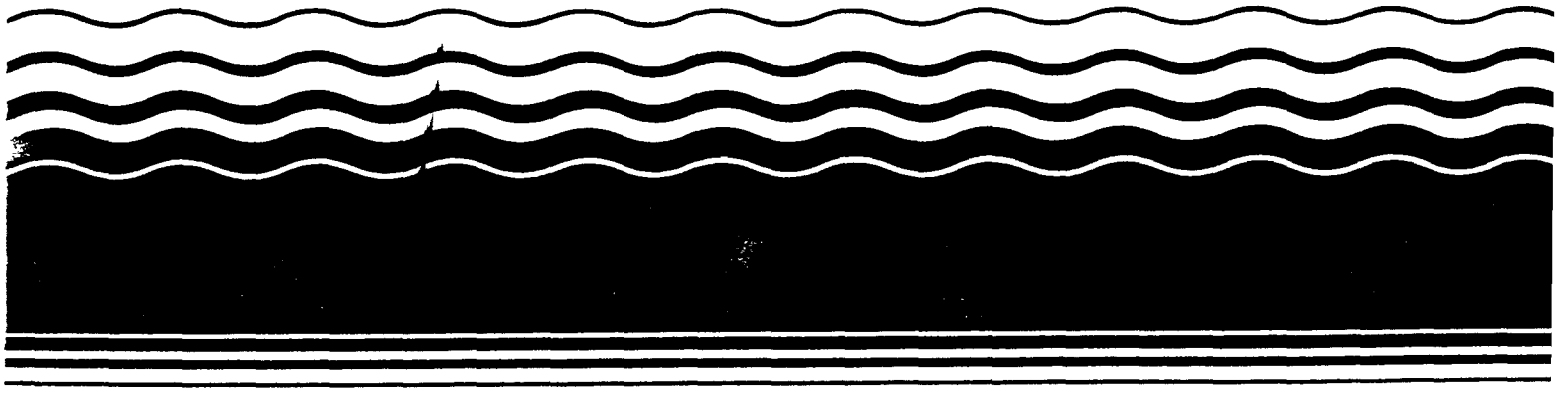
HEALTH EFFECTS ASSESSMENT FOR HEXACHLOROBENZENE



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U.S. Environmental Protection Agency
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DISCLAIMER

This report has been funded wholly or in part by the United States Environmental Protection Agency under Contract No. 68-03-3112 to Syracuse Research Corporation. It has been subject to the Agency's peer and administrative review, and it has been approved for publication as an EPA document. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with hexachlorobenzene. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980a. Ambient Water Quality Criteria Document for Chlorinated Benzenes. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-80-028. NTIS PB 81-117392.

U.S. EPA. 1982. Health and Environmental Effects Profile for Hexachlorobenzene. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1983a. Review of Toxicologic Data in Support of Evaluation for Carcinogenic Potential of Hexachlorobenzene. Prepared by the Carcinogen Assessment Group, OHEA, Washington, DC for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1984. Health Assessment Document for Chlorinated Benzenes. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 600/8-84-015F. NTIS PB 85-150332.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is

assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980b) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983b).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980b). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q_1*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

Hexachlorobenzene has been shown to be carcinogenic in rats, mice and hamsters following oral exposure. Data for humans are not available. U.S. EPA (1980a) derived a q_1^* of 1.688 $(mg/kg/day)^{-1}$ based on the incidence of hepatomas in male Syrian Golden hamsters. This assessment has been extensively peer-reviewed. More recently the U.S. EPA (1984) computed a q_1^* of 1.7 $(mg/kg/day)^{-1}$ based on the incidence of hepatocellular carcinomas in female rats. Data were not available which addressed the potential carcinogenic activity of hexachlorobenzene following inhalation exposure.

ACKNOWLEDGEMENTS

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
BCF	Bioconcentration factor
bw	Body weight
CAS	Chemical Abstract Service
CS	Composite score
GI	Gastrointestinal
LD_{50}	Median lethal dose
LDH	Lactate dehydrogenase
LOAEL	Lowest-observed-adverse-effect level
NOEL	No-observed-effect level
PCT	Porphyria cutanea tarda
ppb	Parts per billion
ppm	Parts per million
SGOT	Serum glutamic oxalacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
TLV	Threshold limit value
TWA	Time-weighted average
w/w	Weight per weight

1. ENVIRONMENTAL CHEMISTRY AND FATE

The relevant physical and chemical properties and environmental fate of hexachlorobenzene (CAS No. 118-74-1) are given as follows:

Chemical class: aromatic	halogenated monocyclic	
Molecular weight:	284.79	(Callahan et al., 1979)
Vapor pressure at 20°C:	1.089×10^{-5} mm Hg	(Callahan et al., 1979)
Water solubility at 25°C:	6 µg/ℓ	(Callahan et al., 1979)
Log octanol/water water partition coefficient:	5.23	(Veith et al., 1979)
Soil mobility:	very slow and the mobility decreases with increase in soil organic content	(U.S. EPA, 1984)
BCF:	22,000 in whole body of fathead minnow (Pimephales promelas)	(U.S. EPA, 1980a)
	7800 in rainbow trout (Salmo gairdneri)	(U.S. EPA, 1980a)
Half-lives in water:	0.3-3.0 days in rivers 30-300 days in lakes and groundwater	(Zoeteman et al., 1980)
Half-life in soil:	3-6 years	(U.S. EPA, 1984)

No estimate of the half-life for hexachlorobenzene in the atmosphere is available in the literature. Based on the available information (Callahan et al., 1979; Singh et al., 1981), significant photodissociation and oxidation of hexachlorobenzene in the atmosphere are unlikely. The likely mechanisms for the removal of significant amounts of hexachlorobenzene from the

atmosphere are rainout and dry deposition (U.S. EPA, 1982). The detection of hexachlorobenzene, an anthropogenic compound, in remote areas (U.S. EPA, 1984) suggests that it may have a long lifetime in order to participate in such long-distance transport from source areas to the remote areas.

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Summaries of studies of absorption of hexachlorobenzene following oral administration were found in U.S. EPA (1980a, 1982, 1984). In many cases details of protocol were lacking and therefore, such studies are not reported here.

According to the U.S. EPA (1980a), intestinal absorption of hexachlorobenzene from aqueous suspension was poor in both rabbits (Parke and Williams, 1960) and rats (Koss and Koransky, 1975). Administration of hexachlorobenzene in cottonseed oil (Albro and Thomas, 1974) or olive oil (Koss and Koransky, 1975) markedly increased absorption from the intestine. Koss and Koransky (1975) showed that intestinal absorption of hexachlorobenzene in rats increased from ~6% to ~80% when the vehicle was changed from water to oil. Zabik and Schemmel (1980) fed hexachlorobenzene (32 mg/kg/day) to female rats by high-fat (45.3% w/w) or high-carbohydrate (67.7% w/w, percentage fat presumed low but not specified) diets. The nutritional adequacy of the diets was not mentioned and no control groups were maintained. Administering hexachlorobenzene in the high-fat diet reportedly resulted in greater accumulation of hexachlorobenzene in (unspecified) tissues and decreased passage of hexachlorobenzene through the GI tract than did administration in the high-carbohydrate diet. The U.S. EPA (1984) suggested that the high-fat diet enhanced GI absorption. It was further suggested (U.S. EPA, 1980a) that dietary hexachlorobenzene selectively partitions into the lipid portion of the diet and that absorption of hexachlorobenzene from lipids is far more rapid and complete than from an aqueous medium.

Ingebrigtsen et al. (1981) administered 10 mg [^{14}C] hexachlorobenzene in peanut oil by gavage to male, bile-duct-cannulated Wistar rats. By 4 days after treatment, 24.8% of the radioactivity had been recovered in the feces. These authors concluded that ~75% of the administered hexachlorobenzene had been absorbed. It should be mentioned that this study did not evaluate absorption of metabolites of hexachlorobenzene resulting from metabolism in the gut, nor was the phenomenon of GI excretion evaluated. Subsequently, Ingebrigtsen and Nafstad (1983) administered 0.4 mg [^{14}C] hexachlorobenzene in peanut oil/kg bw to male Wistar rats and observed peak levels of radioactivity in the liver at 4 hours and in adipose tissue at 24 hours post-treatment. These authors indicated that absorption of hexachlorobenzene from the GI tract, when oil was used as the vehicle, was rapid and fairly complete.

2.2. INHALATION

Pertinent data regarding the absorption of hexachlorobenzene following inhalation exposure could not be located in the available literature.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Reports of subchronic oral exposure of humans to hexachlorobenzene that would be useful in risk assessment were not found in the available literature.

Deichmann (1981) summarized many short-term studies of oral exposure of laboratory rodents to hexachlorobenzene. The primary purpose of these studies was to elucidate the metabolism of hexachlorobenzene and its role in porphyria. Frequently, therefore, only single dosage levels were given, or a sufficiently wide spectrum of toxic manifestations was not reported; therefore, these studies were not useful in risk assessment. Summaries of data from more relevant subchronic oral exposure studies are presented in Table 3-1.

Grant et al. (1974) fed diets containing 10-160 ppm hexachlorobenzene to rats of either sex for 9-10 months. They demonstrated that female rats appeared to be more sensitive to hexachlorobenzene, in that at levels of either 80 or 160 ppm, only females suffered reduced weight gains and porphyria. Males fed diets containing 40 or 60 ppm hexachlorobenzene showed hepatic enzyme induction and increased cytochrome P-450. No effects were reported in rats on diets containing 10 ppm hexachlorobenzene. Kuiper-Goodman et al. (1977) also reported greater sensitivity in female rats; they reported 40% mortality in females (but not males) on diets containing 32 ppm hexachlorobenzene. No effects were observed in rats on diets containing 0.5 ppm (0.025 mg/kg/day). This dietary level was considered a NOEL for rats in this study.

TABLE 3-1

Subchronic Oral Toxicity of Hexachlorobenzene to Laboratory Animals

Species/Strain	Sex/Number	Dose	Dose* (mg/kg/day)	Duration	Effects	Reference
Rat/Sprague-Dawley	M, F/NR	10 ppm diet	0.5	9-10 months	None	Grant et al., 1974
		20 ppm diet	1.0		Pharmacologic action of pentobarbital and zoxazolamine shortened in both sexes	
		40 or 60 ppm diet	2.0 or 3.0		Males only: hepatic aniline hydroxylase, N-demethylase activity, cytochrome P-450 increased	
		80 or 160 ppm diet	4.0 or 8.0		Dose-related increase in relative liver weights and hepatic content of hexachlorobenzene females: reduced weight gains, acquired porphyria	
Rat/COBS	M/70, F/70	0 or 0.5 ppm diet	0.0 or 0.025	15 weeks	None	Kuiper-Goodman et al., 1977
		2 or 8 ppm diet	0.1 or 0.4		Multiple sites of alopecia, scabbing; ataxia with hind leg paresis; hepatomegaly	
		32 ppm diet	1.6		Females only: 40% mortality	
Rat/Wistar	F/36/group	0.5 mg/kg 2 times weekly	0.007	29 weeks	None	Boger et al., 1979
		2.0, 8.0 or 32 mg/kg 2 times weekly	0.03, 0.1 or 0.5		Hepatocellular enlargement, proliferated smooth endoplasmic reticulum, increased glycogen deposits, enlarged mitochondira	
Mice/BALB/c	M/NR	167 ppm diet	21.7	3-6 weeks	Impaired host resistance; IgA reduced; decreased resistance to S. typhosa endotoxin, P. berghei challenge	Loose et al., 1978a,b

TABLE 3-1 (cont.)

Species/Strain	Sex/Number	Dose	Dose* (mg/kg/day)	Duration	Effects	Reference
Rat/Sprague-Dawley	F/10/group	0 ppm diet	0	weaning through two successive litters (~194 days)	None	Kitchin et al., 1982
		60, 80, 100, 120 or 140 ppm diet	3.0, 4.0, 5.0, 6.0 or 7.0		F_{1a}: increasing dose-related mortality of offspring; depressed growth of offspring. F_{1b}: 15-20% reduction in body burden of hexachlorobenzene	
Dog/beagle, 6.3-10.3 kg (mean 8.3 kg)	M, F/NR	1 or 10 mg/dog/day	0.12 or 1.2	up to 12 months	Nodular hyperplasia of gastric tissue	Gralla et al., 1977
		100 mg/dog/day	12		Anorexia, body weight loss, neutrophilia, anemia, hypocalcemia	
		1000 mg/dog/day	120		Mortality, amyloidosis, vasculitis	
Pig/NR	NR/NR	0.05 mg/kg/day	0.05	90 days	None	den Tonkelaar et al., 1978
		0.5 or 5 mg/kg/day	0.5 or 5		"Histopathologic liver changes"	
		50 mg/kg/day	50		Porphyria, hepatomegaly, mortality	
Pig/NR	F/NR	1 ppm diet	0.025	throughout gestation and nursing (~5-6 months)	None	Hansen et al., 1978
		20 ppm diet	0.5		Neutrophilia, gastric irritation, fatty replacement of Brunner's gland, pancreatic periductal fibrosis, hexachlorobenzene accumulation in fat	

*Dosages in mg/kg/day in rats were calculated assuming dietary intake equivalent to 5% of body weight/day; mg/kg/day in mice by assuming a dietary intake equivalent to 13% of body weight/day; in dogs and pigs from data given in the secondary sources.

Beagle dogs appeared to be quite sensitive to hexachlorobenzene. Gralla et al. (1977) exposed male and female beagle dogs to 1, 10, 100 or 1000 mg/dog/day for up to 12 months. Assuming a mean body weight of 8.3 kg, these dosages correspond to 0.12, 1.2, 12 or 120 mg hexachlorobenzene/kg/day. All exposed dogs exhibited nodular hyperplasia of gastric lymphoid tissue. Dosages $\geq$12 mg/kg/day produced anorexia, body weight loss, neutrophilia, anemia, hypocalcemia and hypoglycemia. At 120 mg/kg/day, mortality occurred. A dosage of 0.12 mg/kg/day was designated a LOAEL in this study.

Deichmann (1981) cited a study by den Tonkelaar et al. (1978) in which "histopathological liver changes" were observed in pigs exposed to dosages of 0.5-5 mg hexachlorobenzene/kg/day for 90 days. Apparently, no effects were observed at a dosage of 0.05 mg/kg/day, which defined a NOEL in this study. Hansen et al. (1978) observed neutrophilia, gastric irritation, fatty replacement of Brunner's glands, pancreatic periductal fibrosis and hexachlorobenzene accumulation in the fat of pigs at a dosage of 0.5 mg/kg/day for ~5-6 months.

3.1.2. **Inhalation.** Pertinent data concerning subchronic inhalation of hexachlorobenzene in laboratory animals or man could not be located in the available literature. Reports of occupational exposure to hexachlorobenzene will be discussed in Section 3.2.2.

3.2. CHRONIC

3.2.1. Oral. Accidental ingestion of hexachlorobenzene in humans occurred in Turkey as a result of hexachlorobenzene-treated seed grain being ground into flour and made into bread. More than 600 patients were observed during a 5-year period during which time a total of ~3000 people were affected (Cam, 1959, 1960; Cam and Nigogosyan, 1963). The resultant syndrome, known as PCT, is a manifestation of disturbed porphyrin metabolism and caused blistering and epidermolysis of exposed parts of the body,

particularly the face and hands. Exposure to direct sunlight exacerbated the syndrome; consequently, more cases were examined during the summer. Symptoms subsided after 20-30 days of no exposure. Relapses were common, either as a result of reexposure to contaminated bread or as the result of redistribution of hexachlorobenzene following mobilization from body fat. Other symptoms included hyperpigmentation, hypertrichosis or alopecia (in some cases, permanent), corneal opacities, deformation of the digits, weight loss and a characteristic port wine color of the urine, indicative of porphyria.

A disorder called "pembe yara" or "pink sore" was described in infants of mothers who either had PCT or had eaten hexachlorobenzene-contaminated bread (Cam, 1959, 1960). At least 95% of these children died within a year of birth, and in many villages no children between the ages of 2-5 years survived during the period 1955-1960. It was estimated that PCT and pink sore occurred in individuals who had consumed 50-200 mg hexachlorobenzene/day for a "relatively long period of time" before skin symptoms were manifested.

Deichmann (1981) reported a 20-year follow-up study by Cripps et al. (1978), who reported that affected individuals exhibited the following symptoms; hyperpigmentation, hirsutism, scarring of hands and face, hepatomegaly, ascites, jaundice, recent episodes of red urine, weakness, paresthesia, enlarged thyroid and painless arthritis.

Burns and Miller (1975) conducted an epidemiologic study of 86 residents living or working or both in an area exposed to the production, transportation and disposal of hexachlorobenzene and other chlorinated hydrocarbon wastes in Louisiana. Levels of hexachlorobenzene in plasma were measured and attempts were made to correlate them with demographic characteristics, occupational hazards, food sample analyses and house dust analyses.

Significantly greater ($p<0.05$) hexachlorobenzene levels in plasma were found in male subjects (4.71 ppb) compared with female subjects (2.79 ppb); no effects were associated with race or exposure through consumption of homegrown vegetables or animal food products. Hexachlorobenzene levels in the plasma appeared to be correlated with concentrations in house dust: 68% of the samples from homes of exposed workers contained an average of 380 ppb hexachlorobenzene, compared with 20 ppb in dusts from houses of control subjects.

Few reports have been located in the available literature concerning chronic oral exposure of laboratory animals to hexachlorobenzene. Koss et al. (1978) reported "changes in the histology of the liver and spleen" associated with exposure of rats to 50 mg hexachlorobenzene/kg every other day. Exposure was for 53 weeks. Cabral et al. (1977) exposed male and female Syrian golden hamsters to 50, 100 or 200 ppm hexachlorobenzene in the diet (lifetime exposure) in order to investigate the carcinogenicity of hexachlorobenzene. This study will be reviewed in more detail in Section 4.2. Dose levels employed in these studies were too large to be useful in risk assessment.

3.2.2. Inhalation. Few reports were located in the available literature concerning repeated occupational exposure to hexachlorobenzene. Burns et al. (1974) found hexachlorobenzene levels in blood ranging from 0-310 ppb in 20 spraymen exposed to hexachlorobenzene. These individuals exhibited no signs of PCT; no correlations were observed between blood concentrations of hexachlorobenzene and urinary porphyrin excretion, SGOT, SGPT or serum LDH concentrations. Currier et al. (1980) performed a medical survey of 50 employees exposed to hexachlorobenzene in a chlorinated solvents plant in Louisiana. During various times of this study, TWA air concentrations

ranged from <1-13 ppb. Wipe samples in a control area, laboratory areas and clerical work areas ranged from 0.03-1.24 μg/100 cm^2. Physical examinations and laboratory analyses (hematologic parameters, blood chemistries and urinalyses) did not reveal evidence of PCT. A positive correlation was found between blood concentrations of hexachlorobenzene and the number of years worked in the plant.

Studies on the chronic toxicity of inhalation exposure of hexachlorobenzene to experimental animals could not be located in the available literature.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. A condition known as "pink sore" was described (Cam, 1959, 1960) as occurring in children of mothers affected by the PCT epidemic in Turkey discussed in Section 3.2.1. At least 95% of affected children died within 1 year of birth. It was estimated that the mothers with affected children had consumed 50-200 mg hexachlorobenzene/day for a "relatively long period of time." The presence of hexachlorobenzene in the mothers' milk suggested that pink sore was a manifestation of toxicity due to lactational rather than placental transfer of hexachlorobenzene.

The effects of hexachlorobenzene on fetotoxicity in laboratory animals have been studied by a number of investigators. Grant et al. (1977) exposed groups of 20 female and 10 male weanling Sprague-Dawley rats to diets containing 0, 10, 20, 40, 80, 160, 320 or 640 ppm hexachlorobenzene. At 100 days of age, the F_0 generation was mated to produce the F_{1a} generation. The F_{1a} offspring were weaned at 21 days, and the F_0 rats were again mated after an additional 14-day rest period to produce the F_{1b} generation. The F_{1b} rats were allowed to mature to 100 days and then were mated. This sequence was followed until production of the F_{4b} generation.

The two highest doses (320 and 640 ppm hexachlorobenzene) resulted in 20 and 50% mortality, respectively, of F_0 dams before first whelping. Additionally, the fertility index in rats in these two highest dose groups was reduced, and average litter size was decreased in the F_{1b}, F_{2a} and F_{2b} generations. In these litters from dams exposed to the two highest dietary concentrations of hexachlorobenzene, there was an increase in the number of stillbirths, and all pups born alive were dead within 5 days. From dams fed diets containing 160 ppm hexachlorobenzene, 55% of the pups survived to day 5, but survival to weaning at 21 days was "greatly reduced." The number of live births and survival to weaning were normal in litters from dams exposed to diets containing 80 ppm hexachlorobenzene for the first 2 generations. Subsequent generations suffered an increased incidence of stillbirths, reduced survival and reduced birth weights and weaning weights of offspring. Litters from dams exposed to diets containing 40 ppm hexachlorobenzene experienced only a significantly increased liver weight at weaning (21 days); no other abnormalities were reported. No terata were found in offspring from dams exposed to any dietary level of hexachlorobenzene. Litters from rats fed diets containing <20 ppm hexachlorobenzene seemed normal in all respects. Therefore, 20 ppm in the diet, corresponding to 1 mg hexachlorobenzene mg/kg bw/day (assuming rats consume food equivalent to 5% of their bw/day), was a NOEL for reproductive effects in this study.

Kitchin et al. (1982) exposed groups of 10 female Sprague-Dawley rats to diets containing 0, 60, 80, 100, 120 or 140 ppm hexachlorobenzene. After 96 days of treatment, females were mated to untreated males to produce an F_{1a} generation and were remated 12 days after weaning of the F_{1a} generation.

Fertility and fecundity were not affected by treatment. No terata were reported, but 21-day survival in both generations was reduced, with LD_{50} estimates of 100 and 140 ppm hexachlorobenzene in the maternal diets for the F_{1a} and F_{1b} generations, respectively.

Reduced survival at weaning was attributed by Mendoza et al. (1978) to hexachlorobenzene transmission to nursing pups by milk. These authors fed five Wistar rats diets containing 80 ppm hexachlorobenzene from 2 weeks before mating until whelping. A reciprocal exchange of litters was made with litters from dams not previously treated with hexachlorobenzene. Pups from control dams nursed on hexachlorobenzene-treated dams showed significantly increased liver weights, compared to pups from treated dams nursed on control dams. Mendoza et al. (1978) concluded that hexachlorobenzene exposure by milk had greater effects on the pups than transplacental exposure.

Subsequently, Mendoza et al. (1979) fed Wistar rats diets containing 80 ppm hexachlorobenzene from 2 weeks before mating until 35-36 days after litters were weaned. They reported no marked differences in the external appearance, body weight, liver weight, gestational survival or neonatal survival of litters from treated rats, compared to the litters of controls. Additionally, there were no differences in the number of litters, average number of pups/litter, average number of pups at birth or gestation index, compared to litters from control rats.

Lactational transfer of hexachlorobenzene in rhesus monkeys was investigated by Bailey et al. (1980), who treated three nursing dams for 60 days (presumably starting at parturition) with 64 mg hexachlorobenzene/kg bw/day by gavage. Analyses of the milk from these dams revealed concentrations ranging from 7.51-186 ppm. Hypoactivity and lethargy, progressing to ataxia and death, occurred in one infant by day 29. A second nursing infant died

by day 38. Necropsies revealed congested lungs in one infant, and a subdural hematoma and bilateral hemorrhagic pneumonia in the other. Blood levels (0.42-49.44 ppm hexachlorobenzene) and tissue levels (unreported) in infants were higher than those (0.41-16.16 ppm hexachlorobenzene in blood) in dams. Infants developed clinical signs (unspecified) of toxicity, while dams remained asymptomatic.

Khera (1974) studied the teratogenicity of hexachlorobenzene by treating groups of 7-16 Wistar rats by gavage with 0, 10, 20, 40, 60, 80 or 120 mg hexachlorobenzene in corn oil or 2% aqueous gum tragacanth/kg bw/day during days 6-21 of gestation. Maternal toxicity (manifestations unspecified) and reduced fetal weights resulted from the two highest dosages. A significant increase in the incidence of unilateral or bilateral 14th rib was observed in litters from dams exposed to the two highest dosages of hexachlorobenzene. In this study, 60 mg/kg/day seemed to be a NOEL for teratogenicity.

3.3.2. Inhalation. Reports of effects on reproduction or teratogenicity in humans or animals associated with inhalation exposure to hexachlorobenzene could not be located in the available literature.

3.4. TOXICANT INTERACTIONS

Hayes (1975) stated that porphyria is probably the most frequent and serious cause of photosensitization in man. Some people previously exposed to hexachlorobenzene experience a latent, acute form of porphyria, which is often manifested as cutaneous photosensitization. Acute attacks may be initiated by consumption of alcohol or exposure to barbiturates, which Hayes (1975) interpreted as evidence for synergism of action between hexachlorobenzene and these compounds.

More recently, Teschke et al. (1983) exposed female Wistar rats to 50 ppm hexachlorobenzene in the diet to evaluate the effects of porphyria on hepatic alcohol-metabolizing enzymes. Exposure for 60 days resulted in

porphyria, as evidenced by increased hepatic δ-aminolevulinic acid synthase activity and increased urinary excretion of δ-aminolevulinic acid, porphobilinogen and total porphyrins. Hepatic microsomal ethanol-oxidizing system activities were increased 213%, compared to the activities in nonhexachlorobenzene-exposed controls. Hepatic alcohol dehydrogenase activities remained virtually unchanged. Considering earlier reports that link alcohol consumption with porphyria, Teschke et al. (1983) suggested that high levels of liver acetaldehyde, the result of oxidation of ethanol, may trigger episodes of porphyria and potentiate the action of hexachlorobenzene.

Chadwick et al. (1977) demonstrated that rats exposed to 7.5 mg hexachlorobenzene/kg/day orally for 7 days had increased ability to metabolize and eliminate lindane. Body elimination of lindane increased about 3-fold. Concentrations of lindane in body fat of treated animals were nearly half those in non-hexachlorobenzene-exposed controls following a single oral dose of lindane.

Kluwe et al. (1982) exposed male Sprague-Dawley rats to 30 mg hexachlorobenzene/kg by gavage every 72 hours for seven administrations (20 days). Following treatment, rats were given 0, 0.03, 0.25 or 2.00 mℓ carbon tetrachloride by intraperitoneal injection. Carbon tetrachloride-induced growth retardation, renal tubular function impairment and hepatocellular necrosis were quantitatively greater in hexachlorobenzene-pretreated rats than in non-pretreated rats. Body weight gain was evaluated over a 48-hour period; renal function was evaluated by relative kidney weight, blood urea nitrogen and various urinalysis parameters; and hepatocellular function was evaluated by relative liver weight, serum enzymes and histochemical evaluation.

4. CARCINOGENICITY

4.1. HUMAN DATA

Pertinent data regarding the carcinogenicity of hexachlorobenzene in humans could not be located in the available literature.

4.2. BIOASSAYS

Several studies of the carcinogenicity of hexachlorobenzene administered orally to laboratory animals have been located in the available literature. Smith and Cabral (1980) exposed female MRC Wistar and Agus rats to 100 ppm hexachlorobenzene in their diets for 75 and 95 weeks, respectively. There was an increased incidence of liver cell tumors in both strains of rats, but the statistical significance was not evaluated. Among hexachlorobenzene-exposed MRC Wistar rats, 4/6 developed liver cell tumors, compared to 0/4 of the control group; 14/14 treated Agus rats developed liver cell tumors, compared to 0/12 of the control rats (U.S. EPA, 1983a).

More recently, Lambrecht et al. (1983a,b) fed groups of 94 male and 94 female Sprague-Dawley rats diets containing 0, 75 or 150 ppm hexachlorobenzene. Interim sacrifices for histopathological examination were performed on four rats of each sex/group at 10 intervals up to 64 weeks of treatment. The remaining 58 rats/group were allowed to continue to natural death or until 2 years of treatment. The number at risk was considered to be those surviving at least 12 months, as this was the earliest time to tumor observed.

Based on an average (weighted) food consumption of 22.6 and 16.5 g/rat/day in males and females, respectively, with average adult body weight of 400 and 265 g the low-dose was converted to 4-5 mg/kg/day and the high-dose to 8-9.5 mg/kg/day. The incidence of tumors observed in this study are

presented in Table 4-1. The most striking observations were the high incidences and dose-related incidences of hepatocellular carcinoma in female rats and renal cell adenoma in male rats.

In an earlier study, Lambrecht et al. (1982) exposed rats to dietary concentrations of 0, 200 or 400 ppm hexachlorobenzene for 90 days. Further details of the protocol and statistical analysis are lacking (U.S. EPA, 1983a), but the authors associated treatment with an increased incidence of liver neoplasma, generalized lymphatic leukemias and a variety of renal lesions.

U.S. EPA (1979) exposed Swiss mice of either sex to dietary concentrations of 300, 200, 100, 50 or 0 ppm hexachlorobenzene for 15, 101, 106, 120 or 120 weeks, respectively. An increased incidence of liver cell tumors was observed at dietary concentrations $\geq$100 ppm hexachlorobenzene. Liver cell tumor incidences were 1/16 for males, 1/26 for females; 7/44 for males, 14/41 females; 3/29 for males, 3/30 for females in groups exposed to 300, 200 or 100 ppm hexachlorobenzene, respectively. Liver cell tumors were not observed in mice exposed to 0 or 50 ppm hexachlorobenzene. No other tumors were reported as having an increased incidence in either sex.

Cabral et al. (1977) fed diets containing 0, 50, 100 or 200 ppm hexachlorobenzene to Syrian golden hamsters for life. These diets reportedly (U.S. EPA, 1982) contained 4, 8 or 16 mg/kg/day hexachlorobenzene and resulted in increased rates of alveolar adenomas of the thyroid, hepatomas of the liver and hemangioendotheliomas of both the liver and spleen in male and female hamsters. The incidence of total tumor-bearing animals appeared to be dose-related: 10% of the control group, 56% of the low-dose group, 75% of the middle-dose group and 92% of the high-dose group developed tumors.

TABLE 4-1

Liver and Kidney Tumors in Sprague-Dawley Rats Given Hexachlorobenzene in the Diet for up to 2 years*

Exposure Level	Hepatoma		Hepatocellular Carcinoma		Renal Cell Adenoma		Renal Cell Carcinoma	
	M	F	M	F	M	F	M	F
0	0/54	0/52	0/54	0/52	7/54	1/52	0/54	1/52
Percentage	0	0	0	0	13	2	0	2
75 ppm	10/52	26/56	3/52	36/56	41/52	7/56	0/52	2/46
Percentage	19	46	6	64	79	13	0	4
150 ppm	11/56	35/55	4/56	48/55	42/56	15/54	0/56	2/54
Percentage	20	64	7	87	75	28	0	4

*Source: Lambrecht et al., 1983a,b

Tumor incidence data were highly significant. Probability values for the incidence of hepatomas in male hamsters were 7.5×10^{-7}, 2.45×10^{-15} and 1.3×10^{-19} for low-, middle- and high-dose groups, respectively. In males fed the middle and high concentrations of hexachlorobenzene, probability values were 4.5×10^{-3} and 4.0×10^{-6}, respectively, for the incidence of hepatic hemangioendotheliomas. Probability values for the incidence of hepatomas in females fed low, middle and high dosages were 7.5×10^{-7}, 2.0×10^{-8} and 3.05×10^{-19}, respectively. The probability value for the incidence of hepatic hemangioendotheliomas in middle group females was 0.026.

4.3. OTHER RELEVANT DATA

Very few data concerning the mutagenicity of hexachlorobenzene have been located in the available literature. According to the U.S. EPA (1984), mutagenicity has been observed in Saccharomyces cerevisiae at a minimum concentration of 100 ppm. Lawlor et al. (1979) tested the mutagenic activity of hexachlorobenzene in Salmonella typhimurium strains TA98, TA100, TA1535, TA1537 and TA1538, with and without activation by Aroclor 1254-induced rat hepatic microsomes. Hexachlorobenzene was associated with no detectable mutagenicity in any of the strains tested, with or without metabolic activation. Dosage levels were unspecified.

In a dominant lethal assay, male rats were treated with 0, 70 or 221 mg hexachlorobenzene/kg by gavage for 5 consecutive days. A dose-related depression of male reproductive function occurred, but dominant lethal mutations were not observed (Simon et al., 1979). Khera (1974) also reported a lack of dominant lethal mutations in Wistar rats following gavage administration of 0, 20, 40 or 60 mg hexachlorobenzene/kg for 10 consecutive days.

4.4. WEIGHT OF EVIDENCE

Reports of carcinogenicity of hexachlorobenzene in humans could not be located in the available literature. Smith and Cabral (1980) demonstrated an increased incidence of liver cell tumors in female MRC Wistar and Agus rats exposed to dietary levels of 100 ppm hexachlorobenzene for 75 or 95 weeks. Liver neoplasms were observed in rats exposed to 200 or 400 ppm hexachlorobenzene for 90 days (Lambrecht et al., 1982) and liver and kidney tumors were noted in rats exposed to 75 or 150 ppm in the diet for up to 2 years (Lambrecht et al., 1983a,b). At dietary levels of $\geq$100 ppm for 106 weeks, Swiss mice showed an increased incidence of liver cell tumors (U.S. EPA, 1979). Finally, Cabral et al. (1977) demonstrated significant increases in the incidences of alveolar adenoma of the thyroid, hepatomas of the liver and hemangioendotheliomas of both the liver and spleen in Syrian golden hamsters exposed to hexachlorobenzene. These animal studies provide sufficient evidence that hexachlorobenzene is an animal carcinogen. Thus, according to the criteria for evaluating the overall weight of evidence of carcinogenicity to humans proposed by the Carcinogen Assessment Group of the U.S. EPA (Federal Register, 1984), hexachlorobenzene is most appropriately classified as a Group B2 (Probable Human Carcinogen) chemical.

5. REGULATORY STANDARDS AND CRITERIA

As of March, 1984, neither OSHA nor the ACGIH has set TLVs for hexachlorobenzene in the workroom. The government of Turkey discontinued the use of hexachlorobenzene-treated wheat seed in 1959 (Cam, 1959) after its link with the outbreak of PCT discussed in Section 3.2. Commerical United States production of hexachlorobenzene was discontinued in 1976 (U.S. EPA, 1980a). The Louisiana State Department of Agriculture has set the tolerated level of hexachlorobenzene in meat fat at 0.3 mg/kg (U.S. EPA, 1976). In Australia, the NHMRC has set the limit for hexachlorobenzene in cow's milk at 0.3 mg/kg (Miller and Fox, 1973). WHO has set the tolerated level of hexachlorobenzene in cow's milk at 20 μg/kg (Bakken and Seip, 1976). The New South Wales Department of Health (Australia) has decided that the level of hexachlorobenzene in eggs shall not exceed 0.1 mg/kg (Siyali, 1973). The value of 0.6 μg/kg/day in food was suggested as the upper limit for hexachlorobenzene in food for human consumption (FAO, 1974). The FAO recommendations for residues in foodstuffs were 0.5 mg/kg in fat for milk and eggs and 1 mg/kg in fat for meat and poultry. These data are summarized in Table 5-1.

Based on a q_1^* of 1.688 $(mg/kg/day)^{-1}$ for humans, the resulting water concentration associated with an increased carcinogenic potency is 7.2 ng/ℓ (U.S. EPA, 1980a).

TABLE 5-1

Current Regulatory Standards and Criteria for Hexachlorobenzene

Criterion	Value	Reference
Louisiana State Dept. of Agriculture: Permissible level in meat fat	0.3 mg/kg	U.S. EPA, 1976
NHMRC (Australia): Limit in cow's milk	0.3 mg/kg	Miller and Fox, 1973
WHO: Limit in cow's milk	20 µg/kg	Bakken and Seip, 1976
New South Wales Dept. Health (Australia): Limit in eggs	0.1 mg/kg	Siyali, 1973
FAO/WHO: Limit in food, fat of milk, eggs fat of meat, poultry	0.6 µg/kg/day 0.5 mg/kg 1.0 mg/kg	FAO, 1974
Concentrations in ambient water associated with increased carcinogenic potency	7.2 ng/ℓ	U.S. EPA, 1980a

6. RISK ASSESSMENT

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

Hexachlorobenzene is a chemical associated with several types of malignancies in at least three animal species and for which data are sufficient for derivation of a q_1^*. It is inappropriate, therefore, to derive an AIS for this chemical.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

Hexachlorobenzene is a chemical associated with several types of malignancies in at least three animal species and for which data are sufficient for derivation of a q_1^*. It is inappropriate, therefore, to derive an AIC for this chemical.

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. The U.S. EPA (1980a) based calculation of a q_1^* on the incidence of hepatomas in male Syrian golden hamsters exposed by diet to hexachlorobenzene (Cabral et al., 1977). The q_1^* derived from these data is 1.688 $(mg/kg/day)^{-1}$. More recently, the U.S. EPA (1984) derived a q_1^* of 1.7 $(mg/kg/day)^{-1}$ from data regarding the incidence of hepatocellular carcinoma in female rats (Lambrecht et al., 1983a,b) fed diets containing hexachlorobenzene for up to 2 years. A complete discussion of the computation of the q_1^* is reported in U.S. EPA (1984).

6.3.2. Inhalation. Since no studies of the carcinogenicity of hexachlorobenzene to humans or animals exposed by inhalation have been found in the available literature, no q_1^* can be calculated for inhalation exposure.

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APPENDIX

Summary Table for Hexachlorobenzene

Carcinogenic Potency	Species	Experimental Dose/Exposure	Effect	q_1^*	Reference
Inhalation				ND	
Oral	rat	4-16 mg/kg/day 75 and 150 ppm in diet	hepatocellular carcinoma	1.7 $(mg/kg/day)^{-1}$	Lambrecht et al., 1983a,b; U.S. EPA, 1984

ND = Not derived