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Office of Research and Development
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Environmental Criteria and
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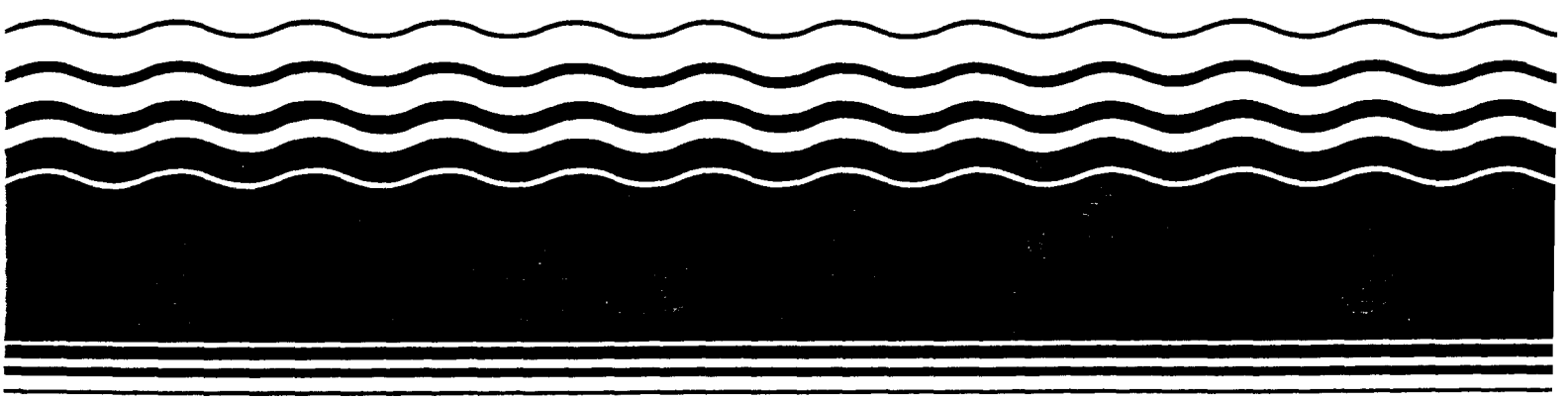
HEALTH EFFECTS ASSESSMENT FOR CHLOROBENZENE



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HEALTH EFFECTS ASSESSMENT FOR CHLOROBENZENE

U.S. Environmental Protection Agency
Office of Research and Development
Office of Health and Environmental Assessment
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Cincinnati, OH 45268

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Office of Solid Waste and Emergency Response
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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 chlorobenzene. 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. 1980b. Ambient Water Quality Criteria for Chlorinated Benzenes. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-80-028. NTIS PB 81-117392.

U.S. EPA. 1982a. Hazard Profile for Chlorobenzene. 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. 1985. 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 (1980a) 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 (1983).

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 (1980a). 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.

The liver and kidneys appear to be target organs for chlorobenzene toxicity. Three separate subchronic oral exposure studies (one in dogs, two in rats) define comparable NOELs. The observed adverse effects indicated a higher sensitivity of the dog to chlorobenzene than the rat. Based on these findings, the highest NOEL of 27.3 mg/kg/day from the dog study (Monsanto, 1967a) was considered appropriate to derive an ADI. The estimated AIC is 1.9 mg/day, estimated by applying an uncertainty factor of 1000. This estimate may be considered to provide adequate protection against adverse human health effects. Long-term (lifetime) animal exposure data are needed to better characterize the toxicity of this compound. A CS of 8 was calculated for the low blood sugar levels, vomiting, diarrhea and conjunctivitis observed in dogs at 55 mg/kg/day.

Subchronic inhalation data from several species are available, but chronic inhalation exposure assessments for chlorobenzene are lacking. A AIC for inhalation exposure has been estimated based upon the lowest subchronic LOAEL reported (75 ppm) (Dilley, 1977). This AIC, 0.4 mg/day, may be conservative. More experimental data are needed addressing lower concentrations and longer durations of exposure to more completely characterize chlorobenzene toxicity.

ACKNOWLEDGEMENTS

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
BCF	Bioconcentration factor
CAS	Chemical Abstract Service
CNS	Central nervous system
CS	Composite score
DNA	Deoxyribonucleic acid
GGTP	γ-Glutamyl transpeptidase
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
ppm	Parts per million
RV_d	Dose-rating value
RV_e	Effect-rating value
SAP	Serum alkaline phosphatase
SGOT	Serum glutamic oxalacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

The relevant physical and chemical properties and environmental fate of chlorobenzene (CAS No. 108-90-7) are as follows:

Chemical class:	monocyclic aromatic (purgeable aromatic)
Molecular weight:	112.56
Vapor pressure:	11.7 mm Hg at 20°C (Mabey et al., 1981)
Water solubility:	466.3 mg/ℓ at 20°C (Horvath, 1982)
Octanol/water partition coefficient:	692 (Hansch and Leo, 1981)
Soil mobility (predicted as retardation factor for soil depth of 140 cm and organic carbon content of 0.087%):	1.9 (Wilson et al., 1981)
BCF:	45.7 (Rainbow trout (muscle); Salmo gairdneri) (Branson, 1978)
	446.7 (Fathead minnow; Pimephales promelas) (Veith et al., 1979)
Half-lives in Air:	3.5 days (Kanno and Nojima, 1979)
Water:	0.3 days in river (Zoeteman et al., 1980)

The half-life of chlorobenzene in soil could not be located in the available literature; however, evaporation is expected to be the predominant loss mechanism from the soil surface (Wilson et al., 1981). The halflife for soil evaporation should be longer than its evaporation half-life from water. In subsurface soil, a fraction of monochlorobenzene may undergo biodegradation, and a fraction may leach through the soil (Wilson et al., 1981).

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

Quantitative studies regarding absorption of chlorobenzene in humans or laboratory animals following ingestion were not located in the available literature. Reports of toxic effects in humans following ingestion or inhalation (Reich, 1934; Rosenbaum et al., 1947; Tarkhova, 1965) suggested absorption by these routes. Deichmann (1981) reported that chlorobenzene absorption from the gastrointestinal tract was facilitated by ingestion of fats and oils. Studies of the metabolism of chlorobenzene in several mammalian species indicated that absorption from the gastrointestinal tract occurred readily (Williams, 1959).

2.2. INHALATION

No quantitative studies regarding absorption in humans or experimental animals following inhalation exposure to chlorobenzene could be located in the available literature. Deichmann (1981) stated that chlorobenzene was absorbed rapidly from the lungs. No supporting data accompanied this statement.

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. No reports of subchronic oral exposure of humans to chlorobenzene could be located in the available literature. Table 3-1 summarizes pertinent subchronic oral exposure data in laboratory animals. Most of these data were taken from summaries provided by Deichmann (1981) and U.S. EPA (1980b, 1985). The studies reviewed by these authors seemed to define similar NOELs: Monsanto Company (1967a) found no effects in dogs exposed by capsule to 27.3 mg/kg/day. Following dietary exposure for 93-99 days, no effects were reported in rats at 50 mg/kg/day (Monsanto Company, 1967b), although slight and inconstant elevated liver and kidney weights were reported at this level in the published version of this study (Knapp et al., 1971). Irish (1963) found no effects in rats given 14.4-18.8 mg/kg/day, 5 days/week, for 192 days.

A study by Varshavskaya (1967) described CNS, liver, hematopoietic and endocrine effects in groups of seven male rats exposed to 0.01 and 0.1 mg chlorobenzene/kg/day by gavage. The U.S. EPA (1980b) considered the results of Varshavskaya (1967) to be questionable primarily because these data suggested effects at dosages far lower than those indicated by other investigators (Table 3-1). Also, data generated by Hollingsworth et al. (1956) in a similar study of the toxicity of o-dichlorobenzene indicated similar effects, but were associated with dosages >3 orders of magnitude greater than those reported by Varshavskaya (1967).

The NTP (1983) conducted 13-week range-finding studies in groups of five male and five female rats and mice with chlorobenzene administered by gavage. Both species were treated with 60, 125, 250, 500 or 750 mg/kg on 5 days/week (transfomed doses 42.9, 89.3, 178.6, 357 and 538 mg/kg bw/day).

TABLE 3-1

Subchronic Oral Toxicity of Chlorobenzene in Experimental Animals

Species	Dose (mg/kg/day)	Duration (days)	Effects	Reference
Dogs (4M, 4F)	27.3	90	none	Monsanto Company, 1967a; Knapp et al., 1971
	54.6	90	diarrhea and vomiting; conjunctivitis	
	272.5	90	mortality 4/8 in 3-5 weeks; increased immature leukocytes, SGOT, bilirubin, cholesterol; decreased blood sugar; histopathological changes in liver, kidneys, spleen	
Rats	12.5 or 50	93-99	none	Monsanto Company, 1967b
	100	93-99	increased liver and kidney weights	
	250	93-99	increased liver and kidney weights; retarded growth in males	
Rats	14.4	192	none	Irish, 1963
	144 and 288 given 5 days/ week	192	increased liver, kidney weights, salivation; partial alopecia	

TABLE 3-1 (cont.)

Species	Dose (mg/kg/day)	Duration (days)	Effects	Reference
Rats	12.5	93-99	none	Knapp et al., 1971
	50 or 100	93-99	increased liver and kidney weights	
	250	93-99	increased liver and kidney weights, retarded growth in males	
Mouse	42.9	13 weeks	one male with hepatic necrosis	NTP, 1983
	89.3	13 weeks	increased liver weights in males; one male with hepatic necrosis	
	178.6	13 weeks	>50% reduction in weight gain, increased excretion of coproporphyrins in females, increased liver weights, lesions of the liver, kidney, bone marrow, spleen and thymus	
	357	13 weeks	100% lethal to males within 1 week, reduced body weight gains, polyuria in females, increased liver weights, lesions of the liver, kidney, bone marrow, spleen and thymus	
	538	10 weeks	100% lethal to males within 1 week and to female mice within 10 weeks, lesions of the liver, kidney, bone marrow, spleen and thymus at death	

TABLE 3-1 (cont.)

Species	Dose (mg/kg/day)	Duration (days)	Effects	Reference
Rat	42.9	13 weeks	none	NTP, 1983
	89.3	13 weeks	none	
	178.6	13 weeks	minimal centrolobular hepatocellular necrosis	
	357	13 weeks	decreased body weight gain, increased GGTP and alkaline phosphatase in females, increased excretion of porphyrins, centrolobular hepatocellular necrosis, nephropathy in males, myeloid depletion of bone marrow	
	538	13 weeks	decreased body weight gain and survival of animals, hematologic effects, increased GGTP and alkaline phosphatase in females, polyuria in males, increased excretion of porphyrins, centrolobular hepatocellular necrosis, nephropathy, lymphoid depletion of thymus and spleen, myeloid depletion of bone marrow	

In mice, 100% lethality to males within 1 week occurred at ≥500 mg/kg, accompanied by histopathological lesions in many organs. All females in the 750 mg/kg group died by week 10. A 50% reduction in body weight gain and histopathological lesions were noted at 250 mg/kg. Increased liver weights in males were noted at 125 mg/kg and liver necrosis was noted in 1 male in the 125 and 1 male in the 60 mg/kg group. Male mice appeared to be affected more severely than females.

In rats, decreased body weight gain in both sexes, altered serum biochemistries in females and histopathological alterations were observed at 500 and 750 mg/kg. Decreased survival was observed at 750 mg/kg. The only effect reported at 250 mg/kg was minimal centrolobular hepatocellular necrosis. No effects were observed at the two lowest levels.

3.1.2. Inhalation. No studies regarding subchronic inhalation exposure of humans to chlorobenzene could be located in the available literature. Because of the potential for being long-term, reports of occupational exposure are discussed in Section 3.2.2.

Several studies of subchronic inhalation exposure of laboratory animals to chlorobenzene have been reviewed by Deichmann (1981) and U.S. EPA (1985) and are summarized in Table 3-2. Dilley (1977) demonstrated small, focal lesions in the adrenal cortex and kidney tubules and decreased SGOT in rats exposed to 75 ppm chlorobenzene 7 hours/day, 5 days/week for 120 days. This dosage, corresponding to an intake of 53 mg/kg/day, defined a LOAEL in rats from inhalation exposure to chlorobenzene. In an earlier study, no effects were seen in rats exposed to 142 mg/kg bw/day for 44 days (Irish, 1963).

Several reports from the foreign literature indicate effects in rats at exposures leading to dosages far below those associated with no effects in

TABLE 3-2

Subchronic Inhalation Toxicity of Chlorobenzene in Experimental Animals

Species	Exposure	Dose[a] (mg/kg/day)	Duration (days)	Effects	Reference
Rats	200 ppm, 7 hours/day, 5 days/week	142	44	none	Irish, 1963
	475 and 1000 ppm, 7 hours/day, 5 days/week	338 and 713	44	increasing severity of hepatomegaly, histopathological changes	
Rats	0.75, 1.50 or 2 mg/ℓ 6 hours/day, 5 days/week	99, 199 or 265	87	none	Monsanto Company, 1978
Rats	0.1 or 1.0 mg/m³ continuous	0.7 or 7.0	72-80	liver necrosis and regenerations; kidney hyperplasia, encephalopathy, pneumonia	Khanin, 1977
Rats	0.1 mg/m³ continuous	0.07	60	none	Tarkhova, 1965
	1.0 mg/m³ continuous	0.7	60	inhibited chronaxia of antigonistic muscles at 39 days; increased blood cholinesterase	
Rats	0.1, 1.25 or 1.5 mg/ℓ[b]	ND	49-98	chronaximetric inhibition	Pislaru, 1960
Rats	0.1 mg/ℓ, 3 hours/day every other day	4.6	259	inhibition of extensor tibialis at 7-14 weeks, normal by 20 weeks	Gabor and Raucher, 1960
Rats	75 or 250 ppm 7 hours/day, 5 days/week	53 or 178	120	focal lesions in adrenal cortex and and kidney tubules; congestion of liver and kidney, decreased SGOT	Dilley, 1977
Rabbits	75 or 250 ppm, 7 hours/day, 5 days/week	102 or 340	120	decreased SGOT	Dilley, 1977
Rabbits	200 ppm, 7 hours/day, 5 days/week	271	44	none	Irish, 1963
Guinea pigs	200 ppm, 7 hours/day, 5 days/week	102	44	none	Irish, 1963

TABLE 3-2 (cont.)

Species	Exposure	Dose[a] (mg/kg/day)	Duration (days)	Effects	Reference
Dogs	0.75 mg/ℓ, 6 hours/day, 5 days/week	15.8	87	none	Monsanto Company, 1978
	1.50 mg/ℓ, 6 hours/day, 5 days/week	31.6	87	weight loss, conjunctivitis, moribund by 31 days	
	200 mg/ℓ, 6 hours/day, 5 days/week	4218	87	weight loss, hypoactivity and conjunctivitis; vacuolated hepatocytes, cytoplasmic vacuolation of renal tubules, bilateral atrophy of seminiferous tubules; leukocytopoenia; elevated SAP, SGOT, SGPT; aplastic bone marrow, mortality in 5/8 dogs by 25-29 days	

[a]Dose in mg/kg was calculated assuming the following inhalation rates and body weights: rats - 0.26 m³/day and 0.35 kg; rabbits - 1.6 m³/day, 1.13 kg; guinea pigs - 0.23 m³/day, 0.43 kg; dogs - 1.5 m³/day, 12.7 kg

[b]Exposure data insufficient for calculation of dose

ND = Not derived because exposure data are insufficient

reports from the domestic literature. For example, Khanin (1977) reported histopathological lesions in several organs at 0.7 mg/kg bw/day. Neuromuscular dysfunction was reported in rats at exposures leading to dosages of 0.7-4.6 mg/kg bw/day (Tarkhova, 1965; Pislaru, 1960; Gabor and Raucher, 1960). In the absence of corroborating evidence from the domestic literature, the data are not considered reliable for use in risk assessment.

In subchronic inhalation experiments in other species, no adverse effects were observed in rabbits at 102-340 mg/kg bw/day (Dilley, 1977; Irish, 1963), in guinea pigs at 102 mg/kg bw/day (Irish, 1963) or in dogs at 15.8 mg/kg bw/day (Monsanto Company, 1978). Dogs appear to be the most sensitive species tested, however, as weight loss and moribundity occurred in this species by 31 days of exposure to 31.6 mg/kg bw/day (Monsanto Company, 1978).

3.2. CHRONIC

3.2.1. Oral. No reports of chronic oral exposure of humans to chlorobenzene could be located in the available literature. Minimal toxicity data are available from the 103-week carcinogenicity bioassay in rats and mice (NTP, 1983). Groups of 50 male and 50 female B6C3F_1 mice were treated by gavage with chlorobenzene in corn oil at 0, 60 and 120 mg/kg for females and 0, 30 and 60 mg/kg for males. Groups of 50 male and 50 female F344/N rats were treated with 0, 60 and 120 mg/kg. Treatments were performed 5 days/week for 103 weeks. Both untreated and vehicle-treated controls were maintained.

Neither mice nor rats had clinical signs of toxicity related to treatment with chlorobenzene. Statistically significant reduced survival was observed in low-dose male mice and high-dose male rats. Increased body weights in both treated groups of female rats were noted during the second

year of the experiment. No histopathologic evidence of toxicity was was observed in mice; however, rats had "equivocal evidence for mild chlorobenzene-induced hepatocellular necrosis."

3.2.2. Inhalation. The only available reports of chronic human exposure to monochlorobenzene were summaries by U.S. EPA (1985) and Deichmann (1981), from which this discussion was adapted. Girard et al. (1969) reported the case of a 70-year-old woman exposed for 6 years to a glue containing 70% chlorobenzene. From the time she began using the glue, she experienced headaches and irritation of the mucosa of the upper respiratory tract and eyes. After 6 years, she had developed medullary aplasia. No exposure data were available.

Rosenbaum et al. (1947) examined 28 factory workers, many of whom complained of headaches and showed signs of somnolescence and dyspepsia. Other complaints included tingling, numbness and stiffness of the extremities (8 workers), hyperesthesia of the hands (4 workers), and spastic contractions of the finger muscles (9 workers) or of the gastrocnemius (2 workers). These workers had reportedly been exposed for 1-2 years, but details of exposure were not specified. No neurotoxic signs were displayed by 26 workers exposed to benzene and/or chlorobenzene fumes for <1 year.

No reports of chronic inhalation exposure of laboratory animals to chlorobenzene could be located in the available literature.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

No reports of fetotoxicity or teratogenicity in humans or animals associated with either oral or inhalation exposure to chlorobenzene could be located in the available literature.

3.4. TOXICANT INTERACTIONS

No pertinent data confirming the interaction of chlorobenzene with other xenobiotics could be located in the available literature. Generalizing that the halogenated benzenes appeared to increase the activity of microsomal cytochrome P-450-dependent enzyme systems, the U.S. EPA (1980b) suggested that exposure to chlorobenzene might be expected to hasten metabolism of other xenobiotics to either more or less toxic metabolites.

Shelton and Weber (1981) investigated the hepatotoxicity of a 1:38 molar ratio mixture of carbon tetrachloride and chlorobenzene in male CF-1 mice. The dosages used (not specified) were given by intraperitoneal injection. Although parameters of hepatotoxicity were not mentioned, the U.S. EPA (1985) stated that the dose-response did not deviate from that predicted by addition alone.

4. CARCINOGENICITY

4.1. HUMAN DATA

No reports associating chlorobenzene with cancer in humans could be located in the available literature.

4.2. BIOASSAYS

The NTP (1983) conducted a study of the carcinogenicity of chlorobenzene in rats and mice. Based on data from a 13-week dose range-finding experiment, 50 rats of each sex were treated by gavage with 60 or 120 mg/kg, 5 days/week for 103 weeks. Both untreated and vehicle-treated control groups of 50 rats of each sex were maintained.

Throughout the study, body weight of treated and control animals remained comparable. Survival rates were similar until about 70 weeks of treatment, at which time survival in high-dose group males was significantly reduced. Survival at the end of 2 years was 68, 78, 64 and 52% in untreated control, vehicle-treated control, low-dose and high-dose males, respectively. Among female rats, 2-year survival data were 74, 58, 60 and 62% in untreated control, vehicle-treated control, low-dose and high-dose groups, respectively.

Although there was some disagreement in the interpretation of liver lesions, pathologists evaluating the slides seemed to agree that inflammation and cytoplasmic basophilia, manifestations of hepatic degeneration, were less severe in chlorobenzene-treated rats than in the control groups. In male rats, a significant increase in neoplastic nodules in the liver was observed in the high-dose group (Table 4-1) as determined by both the incidental tumor test ($p=0.021$) and the Cochran-Armitage test for dose-related trend ($p=0.043$). Liver carcinomas in male rats were found only in the vehicle-treated group (2/50). Combining the incidences of neoplastic

TABLE 4-1

Statistical Comparisons of Liver Tumors in Male Rats
Treated with Chlorobenzene*

Tumor Type	Untreated Control	Vehicle Control	60 mg/kg	120 mg/kg
Neoplastic nodule	4/50 (8%)	2/50 (4%)	4/49 (8%)	8/49 (16%)
Incidental tumor test		p=0.011	p=0.290	p=0.021
Cochran-Armitage test		p=0.027	NA	NA
Fisher exact test		NA	p=0.329	p=0.043
Carcinoma	0/50 (0%)	2/50 (4%)	0/49 (0%)	0/49 (0%)
Incidental tumor test		p=0.139	p=0.283	p=0.331
Cochran-Armitage test		p=0.098	NA	NA
Fisher exact test		NA	p=0.253	p=0.253
Neoplastic nodule or carcinoma	4/50 (8%)	4/50 (8%)	4/49 (8%)	8/49 (16%)
Incidental tumor test		p=0.054	p=0.570	p=0.083
Cochran-Armitage test		p=0.121	NA	NA
Fisher exact test		NA	p=0.631	p=0.168

*Source: NTP, 1983

NA = Not applicable

nodules and carcinomas failed to create an overall tumor incidence that was statistically significant. There was no evidence of neoplastic nodule or liver tumor formation in female rats.

The incidence of pituitary tumors (adenoma, adenocarcinoma and carcinoma) in both male and female rats was found to be significantly inversely related to treatment with chlorobenzene (Table 4-2).

The carcinogenicity of chlorobenzene has also been tested in $B6C3F_1$ mice (NTP, 1983). Males were treated with 30 or 60 mg/kg and females were subjected to 60 or 120 mg/kg, 5 days/week for the 2-year (103-week) treatment period. These dosages were chosen on the basis of a preliminary 13-week dose range-finding study. It appeared that the doses chosen for the chronic bioassay were too low based on the data generated by the 13-week preliminary study, and that the accepatable intake had not been approached (U.S. EPA, 1985). No tumors occurred with frequencies that differed significantly from those in the control groups.

The U.S. EPA (1985) stated that the data generated by these studies were not sufficient to draw conclusions about the carcinogenicity of chlorobenzene.

4.3. OTHER RELEVANT DATA

Studies of the mutagenicity of chlorobenzene in microorganisms have yielded mixed results, with positive results observed only in tests with Saccharomyces cerevisiae (Simmon et al., 1979) and Streptomyces antibioticus (Keskinova, 1968) (Table 4-3).

In a sex-linked recessive lethal test in Drosophila melanogaster (Bioassay Systems Corp., 1982), male flies were exposed to 36,000 or 128,400 ppm of chlorobenzene for 1 hour. The exposed flies were mated at 1-3 days

TABLE 4-2

Pituitary Tumors in Male Rats Treated with Chlorobenzene*

Tumor Type	Untreated Control	Vehicle Control	60 mg/kg	120 mg/kg
Adenoma	20/49 (41%)	10/50 (20%)	9/42 (21%)	3/47 (6%)
Incidental tumor test		p=0.109	p=0.532	p=0.101
Cochran-Armitage test		p=0.047	NA	NA
Fisher exact test		NA	p=0.534	p=0.046
Adenoma, adenocarcinoma or carcinoma	20/49 (41%)	12/50 (24%)	9/42 (21%)	3/47 (6%)
Incidental tumor test		p=0.044	p=0.462	p=0.044
Cochran-Armitage test		p=0.016	NA	NA
Fisher exact test		NA	p=0.484	p=0.015

*Source: NTP, 1983

NA = Not applicable

TABLE 4-3

Mutagenicity Testing of Chlorobenzene*

Test System	Metabolic Activation	Concentration	Result	Reference
Asperigillus nidulans	-	200 µg/mℓ	negative	Prasad, 1970
Salmonella strains TA1535, TA1537, TA1538, TA92, TA98, TA100	±	0.1-0.5 µℓ/plate	negative	Simmon et al., 1979
Salmonella typhimurium strains	±	100 µg/plate	negative	Merck and Company, 1978
Saccharomyces cerevisiae	±	0.05-6%	positive	Simmon et al., 1979
S. cerevisiae	±	0.01-5 µℓ/plate	negative	Monsanto Company, 1976
Mouse lymphoma L5178Y (forward mutation of TK)	- +	0.001-0.1 µℓ/mℓ 0.0001-0.01 µℓ/mℓ	negative negative	Monsanto Company, 1976
Escherichia coli ($polA^+/polA^-$)	-	10-20 µℓ/plate	negative	Simmon et al., 1979
Bacillus subtilis (rec^-/rec^+)	-	10-20 µℓ/plate	negative	Simmon et al., 1979
Streptomyces antibioticus	-	NR	positive	Keskinova, 1968

*Source: U.S. EPA, 1985

NR = Not reported

(to sample effects on spermatozoa), 4-5 days (to sample effects on spermatids) and 6-7 days (to measure effects on spermatocytes) after exposure. No evidence of mutagenicity was found in 11,543 chromosomes from treated flies compared to 9430 chromosomes from control flies.

A positive response was obtained in a test for in vitro induction of chromosomal aberrations in Chinese hamster ovary cells (U.S. EPA, 1982b). Concentrations of 444, 266 and 178 µg/mℓ were tested in assays not incorporating a metabolic activating system and concentrations of 493, 296, 197 and 99 µg/mℓ were assayed with an S-9 activating system. A positive response was observed in the S-9 activated system after a 4-hour exposure but not after a 2-hour exposure.

4.4. WEIGHT OF EVIDENCE

No evidence of carcinogenicity associated with exposure to chlorobenzene in humans could be located in the available literature. The NTP (1983) bioassay failed to confirm or deny the carcinogenicity of chlorobenzene in rats or mice. IARC has not evaluated the risk to humans associated with oral or inhalation exposure to chlorobenzene. By applying the criteria proposed by the Carcinogen Assessment Group of the U.S. EPA for evaluating the overall weight of evidence for carcinogenicity to humans (Federal Register, 1984), a designation of chlorobenzene as a Group D - Not Classified chemical seems most appropriate.

5. REGULATORY STANDARDS AND CRITERIA

A summary of regulatory standards and criteria for chlorobenzene is presented in Table 5-1. Both the ACGIH (1980) and NIOSH (1982) have set the TWA for chlorobenzene at 75 ppm. No STEL has been set.

The U.S. EPA (1980b) has suggested an ambient water quality criterion of 488 µg/ℓ to protect human health. This criterion is based on an ADI of 1.008 mg/day, assumes consumption of 2 ℓ water/day and takes into consideration consumption by fish and shellfish.

TABLE 5-1

Current Regulatory Standards and Criteria for Chlorobenzene

Standard or Criterion	Value	Reference
TLV	75 ppm (~350 mg/m^3)	ACGIH, 1980
TWA	75 ppm	U.S. EPA, 1985
Ambient water quality criteria:		
Freshwater aquatic life		
Acute toxicity	250 µg/ℓ	U.S. EPA, 1985
Saltwater aquatic life		
Acute toxicity	160 µg/ℓ	U.S. EPA, 1985
Chronic toxicity	129 µg/ℓ	U.S. EPA, 1985
Ambient water quality criterion:		
Human life	488 µg/ℓ	U.S. EPA, 1985
Organoleptic	20 µg/ℓ	U.S. EPA, 1985

6. RISK ASSESSMENT

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

6.1.1. Oral. NOAELs from subchronic oral studies include 14.4 mg/kg/day in rats (Irish, 1963), 50 mg/kg/day in rats (Monsanto Company, 1967b), 89.3 mg/kg/day in rats (125 mg/kg, 5 days/week) (NTP, 1983), 12.5 mg/kg/day in rats (Knapp et al., 1971) and 27.3 mg/kg/day in dogs (Monsanto Company, 1967a; Knapp et al., 1971). The Irish (1963) study reported a NOEL of 14.4 mg/kg/day and LOAEL of 144.4 mg/kg/day, however, intermediate doses were not evaluated. The Monsanto (1967a,b) study defined a NOAEL of 50 mg/kg/day and LOAEL of 100 mg/kg/day in the rat. In contrast, a NOEL of 27.3 mg/kg/day and a LOAEL of 55 mg/kg/day were defined for the dog. The observed adverse effects indicated a higher sensitivity of the dog to chlorobenzene than the rat. Based on these findings the highest dog NOEL of 27.3 mg/kg/day (Monsanto, 1967b) was considered appropriate to derive an ADI for subchronic exposure. An uncertainty factor of 100 is applied, a factor of 10 to account for interspecies extrapolation and a factor of 10 to provide greater protection for especially sensitive populations. Assuming a body weight in man of 70 kg, an AIS for man can be calculated as follows:

$$\text{AIS} = (27.3 \text{ mg/kg/day days} \times 70 \text{ kg}) \div 100$$
(the uncertainty factor derived above)

$$\text{AIS} = 19.1 \text{ mg/day}$$

In dogs immature leukocytes, low blood sugar, conjunctivitis, vomiting and diarrhea were reported at 55 mg/kg/day, whereas higher doses caused mortality and histopathological lesions in liver and kidneys (Monsanto, 1967a). A human MED was calculated by multiplying the dog MED by the cube root of the ratio of the body weight of dogs (assumed: 12.7 kg) to that of humans (assumed: 70 kg) and dividing the result by 10, an uncertainty

factor chosen to reflect the unknowns in extrapolating from a subchronic study to chronic application. The result, 3.1 mg/kg/day, is multiplied by 70, resulting in an MED of 218 mg/day for a 70 kg man. This MED corresponds to an RV_d of 2.0; the effects of vomiting, diarrhea, conjunctivitis and immature luekocytes rate an RV_e of 4. A CS of 8, the product of RV_d and RV_e, is calculated.

6.1.2. Inhalation. No pertinent data regarding the effects of subchronic inhalation exposure of humans to chlorobenzene could be located in the available literature. Studies by Irish (1963) defined NOELs in rats, rabbits and guinea pigs of 142, 271 and 102 mg/kg/day, respectively. Dilley (1977) found small focal lesions in the adrenal cortex and kidney tubules, congestion of the liver and kidney, and decreased SGOT in rats exposed to 75 ppm chlorobenzene for 7 hours/day, 5 days/week for 120 days. This concentration resulted in an intake of 53 mg/kg/day (applying the assumptions stated in Table 3-2), which was designated as a LOAEL in this study. An interim AIS can be calculated from these data by assuming a body weight of man of 70 kg and using an uncertainty factor of 1000; a factor of 10 to account for interspecies conversion, another factor of 10 to convert from a LOAEL to a NOEL and a final factor of 10 to afford greater protection to unusually sensitive populations. The resultant interim AIS is 3.7 mg/day.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

6.2.1. Oral. No reports of chronic oral exposure of humans or animals to chlorobenzene could be located in the available literature. An interim AIC for chronic oral exposure can be derived from the subchronic AIC by applying an additional uncertainty factor of 10 to convert from a subchronic study to chronic exposure; this results in an overall uncertainty factor of 1000. The resultant AIC is 1.9 mg/day.

6.2.2. Inhalation. No reports of chronic exposure of humans to chlorobenzene that were satisfactory for risk assessment, or studies of chronic animal exposure could be located in the available literature. The study by Dilley (1977), used to derive an AIS, can be used to derive an AIC for inhalation exposure. An additional uncertainty factor of 10 to account for derivation of an AIC from subchronic data results in an AIC of 0.4 mg/day, starting with the AIS of 3.7 mg/day (see Section 6.1.2).

6.3. CARCINOGENIC POTENCY (q_1^*)

6.3.1. Oral. The NTP (1983) bioassay failed to demonstrate conclusively the carcinogenicity, or lack of carcinogenicity, of chlorobenzene administered to rats and mice by gavage. No other reports of carcinogenicity in humans or animals resulting from oral exposure to chlorobenzene could be located in the available literature. Therefore, insufficient data are available from which to estimate carcinogenic potency.

6.3.2. Inhalation. No reports of carcinogenicity in humans or animals associated with inhalation exposure to chlorobenzene could be located in the available literature; hence, no estimation of carcinogenic postency has been made.

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APPENDIX

Summary Table for Chlorobenzene

	Species	Experimental Dose/Exposure	Effect	Acceptable Intake (AIS or AIC)	Reference
Inhalation					
AIS	rat	53 mg/kg/day	focal lesions in liver, kidney tubules; hepatic and renal congestion; decreased SGOT	3.7 mg/day	Dilley, 1977
AIC	rat	53 mg/kg/day	focal lesions in liver, kidney tubules; hepatic and renal congestion; decreased SGOT	0.4 mg/day	Dilley, 1977
Oral					
AIS	dog	27.3 mg/kg/day for 90 days	none	19.1 mg/day	Monsanto, 1967a
AIC	dog	27.3 mg/kg/day for 90 days	none	1.9 mg/day	Monsanto, 1967a
Maximum composite score	dog	55 mg/kg/day for 90 days (RV_d = 2.0)	immature leukocytes, conjunctivitis, vomiting and diarrhea (RV_e=4)	8	Monsanto, 1967a

ND = Not derived