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GREAT LAKES WATER QUALITY INITIATIVE
HUMAN HEALTH CRITERIA DOCUMENTS

TERMS AND VALUES USED IN THE GREAT LAKES WATER QUALITY INITIATIVE CRITERIA DOCUMENT

TERM	ABBREV.	VALUE
Human noncancer criterion/value	HNC/HNV	Varies by chemical
Human cancer criterion/value	HCC/HCV	Varies by chemical
Acceptable daily exposure	ADE	Varies by chemical
Risk associated dose	RAD	Varies by chemical
Cancer slope factor	q1*	Varies by chemical
Risk level	---	1×10^{-5}
No observed adverse effect level	NOAEL	Varies by chemical
Lowest observed adverse effect level	LOAEL	Varies by chemical
Uncertainty factor	UF	Varies by chemical
Body weight	BW	70 kg, except 65 kg for mercury
Relative source contribution	RSC	0.80 noncarcinogens 1.00 carcinogens
Water consumption - Drinking water and incidental exposure	WC_d	2 liters/day
Water consumption - Incidental exposure	WC_r	0.01 liter/day
Fish consumption trophic level 3 fish	FC_{TL3}	0.0036 kg/day
Fish consumption trophic level 4 fish	FC_{TL4}	0.0114 kg/day
Bioaccumulation factor for trophic level 3	BAF_{TL3}	Varies by chemical, expressed as L/kg
Bioaccumulation factor for trophic level 4	BAF_{TL4}	Varies by chemical, expressed as L/kg

Criteria are rounded to two significant figures and are expressed in ug/L. BAFs are taken from the Technical Support Document for Bioaccumulation Factors which is available in the docket for the final Great Lakes Water Quality Initiative.

GREAT LAKES WATER QUALITY INITIATIVE
TIER I HUMAN HEALTH CRITERIA FOR
BENZENE
CAS NO. 71-43-2

Tier 1 Human Noncancer Criterion

Acute exposure to benzene vapors by humans is often associated with neurotoxicity characterized by loss of sensation, vertigo, headache and depression of the central nervous system. Hematopoietic toxicity involving changes in the bone marrow, spleen, and thymus has been associated with benzene exposure. Benzene has also been found to cause embryo/fetotoxicity in experimental animals (EPA, 1980).

There are few chronic or oral studies available which examine the noncarcinogenic effects of benzene. The subchronic oral study by Wolf et al. (1956) was considered appropriate for Tier 1 HNC derivation. In this study, female Wistar rats in groups of 10 were administered benzene in olive oil by gavage for 5 days/week for six months. A group of 20 rats served as controls. Dose levels were 0, 1, 10, 50, and 100 mg/kg/bw/day. During this period hematologic examinations were performed on selected animals. Growth, body weight, organ weights, behavior, urea nitrogen in blood, histopathological changes and bone marrow counts were also evaluated. Rats exposed to 50 and 100 mg/kg/day exhibited leukopenia and erythrocytopenia, whereas these effects were marginal in the 10 mg/kg/day group. The 1 mg/kg/day dose level was considered the NOAEL for this study. This dose is equivalent to 0.71 mg/kg/day after being adjusted for exposure for only 5 days/week.

The findings of the Wolf et al. (1956) study are supported by the results of a chronic study by NTP (1986). In this study, C57BL16N mice and F344 rats (50 animals/sex/group) were administered benzene orally at doses of 0, 50, 100 or 200 mg/kg, 5 days/week, for 103 weeks. An additional group consisting of female rats and mice of both sexes were administered 25 mg/kg. Blood was taken for analysis from 10 animals/sex/group at various times during the study. The results of the study showed dose-related leukopenia in rats and mice of each sex for the first 18 months of the study. However, at 24 months, the numbers of white blood cells in high dose male rats, high dose female rats, and mid-dose male mice were higher than controls. Numbers of white blood cells in dosed female mice were not significantly different from controls.

Hematopoietic toxicity of benzene following exposure via inhalation was reported by Deichmann et al. (1963). In this study, groups of male and female Sprague-Dawley rats were exposed 5 hours/day, 4 days/week, for periods ranging from 5 weeks to 7 months, to benzene concentrations of 0, 15, 29, 31, 44, 47, 61, 65, or 831 ppm. Several hematologic parameters, and other parameters including body weight, food intake and blood benzene

levels were determined periodically during the study. Following 2-4 weeks of exposure, groups exposed to benzene concentrations of 61 to 831 ppm demonstrated a significantly increased level of leukopenia. Hematopoietic effects were moderate in groups exposed to 44 to 47 ppm for 5-8 weeks. Exposure to 31 ppm benzene for over 4 months did not induce changes in the hematopoietic system and was considered a NOAEL for this study. Based on the conditions of exposure and an assumed absorption factor of 50% (EPA, 1987), a NOAEL of 2.35 mg/kg/day was calculated. This value is comparable to the value calculated in the Wolf et al. (1956) study.

EPA (1985) suggested that the Wolf et al. (1956) and Chang (1972) studies could be used to establish a range of acceptable daily intake (ADI) values. In the Chang (1972) study 119 workers occupationally exposed to benzene were examined. Hematological abnormalities were reported in 28 of the workers. These abnormalities included 21 workers with anemia, 2 with leukopenia, and 5 with anemia and leukopenia. Based on an estimate of exposure duration and benzene concentration, the researcher derived an exponential function which suggested a threshold level of 10 ppm for hematologic effects. This study was not used for criterion development due to the absence of reliable data on the actual exposure concentrations for the individual employees.

Rozen et al. (1984) examined the effect of inhalation exposure to 0, 10, 31, 100 and 301 ppm benzene on B- and T-lymphocyte mitogen-induced blastogenesis in C57B1 mice. Exposure to benzene at all doses for 6 hours/day for 6 days resulted in a significant depression in femoral lipopolysaccharide (LPS)-induced B-colony forming ability while total numbers of B-lymphocytes were significantly depressed at 100 and 300 ppm. Splenic phytohemagglutinin (PHA)-induced blastogenesis was significantly depressed at 31, 100 and 300 ppm while total numbers of T-lymphocytes were significantly depressed at 100 and 300 ppm. This study was not used for risk assessment because it used the inhalation route of exposure and it is questionable whether the effects produced in this study are biologically significant and adverse.

Few studies using the oral route of exposure have examined the reproductive/developmental effects of benzene. Nawrot and Staples (1979) administered 0.3, 0.5 or 1.0 ml/kg/day (790, 1320 and 2640 mg/kg/day, respectively) benzene to pregnant CD-1 mice during days 6-15 or 12-15 of gestation. Despite some maternal lethality and embryonic resorptions at the two higher doses, no evidence of teratology was seen.

$$ADE = \frac{NOAEL}{UF} = \frac{0.71\ mg/kg/d}{1000} = 7.1 \times 10^{-4}\ mg/kg/d$$

Where: Uncertainty Factor = 1000, composed of:
10x for interspecies variability
10x for intraspecies differences
10x for subchronic exposure duration

Drinking Water Sources:

$$HNV = \frac{ADE \times BW \times RSC}{WC_d + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{7.1 \times 10^{-4} \text{ mg/kg/d} \times 70 \text{ kg} \times 0.8}{2 \text{ l/d} + [(0.0036 \times 3) + (0.0114 \times 5)]}$$

$$= 19 \text{ ug/L}$$

Non-Drinking Water Sources:

$$HNV = \frac{ADE \times BW \times RSC}{WC_r + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{7.1 \times 10^{-4} \text{ mg/kg/d} \times 70 \text{ kg} \times 0.8}{0.01 \text{ l/d} + [(0.0036 \times 3) + (0.0114 \times 5)]}$$

$$= 5.1 \times 10^{2} \text{ ug/L}$$

References:

Chang, I.W. 1972. Study on the threshold limit value of benzene and early diagnosis of benzene poisoning. J. Cath. Med. Coll. 23:429.

Deichmann, W.B., W.E. MacDonald. and E. Bernal. 1963. The hematopoietic tissue toxicity of benzene vapors. Toxicol. Appl. Pharmacol. 5:201-224.

International Agency for Research on Cancer (IARC). 1982. IARC Monograph: Evaluation of the Carcinogenic Risk of Chemicals to Humans, Volume 29, WHO Publications Center, USA, Albany, NY, pp 1-416.

National Toxicology Program (NTP). 1986. Toxicology and Carcinogenesis Studies of Benzene in F344/N Rats and B6C3F1 Mice (Gavage Studies). NTP Technical Report Series. 289., National Toxicology Program, Research Triangle Park, NC.

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Rozen, M.G., C.A. Snyder, and R.E. Albert. 1984. Depressions in B- and T-lymphocyte mitogen-induced blastogenesis in mice exposed to low concentrations of benzene. Toxicol. Letters. 20:343-349.

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Tier 1 Human Cancer Criterion

According to the weight-of-evidence method for the classification of carcinogens, benzene is a Class A carcinogen (known human carcinogen) (IARC, 1982; EPA, 1987; 1989). This is based on sufficient evidence from epidemiologic studies on the incidence of non-lymphocytic leukemia from occupational exposure, and increased incidence of neoplasms in rats and mice exposed to benzene by inhalation and gavage (EPA, 1987). In addition, numerous studies have found a significant increase in chromosomal aberrations of bone marrow cells and peripheral lymphocytes from workers exposed to benzene (IARC, 1982). The data are sufficient to derive a Tier 1 HCC for benzene.

Numerous epidemiologic and case studies have shown a relationship between leukemia and exposure to benzene (IARC, 1982). The oral slope factor for benzene based on human data is estimated to be 2.9E-2 $(mg/kg/day)^{-1}$ (EPA, 1987). The unit risk estimate is based on the geometric mean of four maximum likelihood point estimates using pooled data from the studies of Rinsky et al. (1981) and Ott et al. (1978), which was then adjusted for the results from the Wong et al. (1983) study as described by EPA (1987).

The slope factor (q1*) of the dose-response curve for the carcinogenic effects of benzene by the oral route, 2.9E-2 $(mg/kg/day)^{-1}$ is used in the calculation of the HCC for benzene.

$$RAD = \frac{\text{Risk Level}}{q1^*} = \frac{1 \times 10^{-5}}{2.9 \times 10^{-2}\ (mg/kg/d)^{-1}}$$

$$= 3.448 \times 10^{-4}\ mg/kg/d$$

Drinking Water Sources:

$$HCV = \frac{RAD \times BW}{WC_d + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{3.448 \times 10^{-4} \text{ mg/kg/d} \times 70 \text{ kg}}{2 \text{ l/d} + [(0.0036 \times 3) + (0.0114 \times 5)]}$$

$$= 12 \text{ ug/L}$$

Non-Drinking Water Sources:

$$HCV = \frac{RAD \times BW}{WC_r + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{3.448 \times 10^{-4} \text{ mg/kg/d} \times 70 \text{ kg}}{0.01 \text{ l/d} + [(0.0036 \times 4) + (0.0114 \times 5)]}$$

$$= 3.1 \times 10^{2} \text{ ug/L}$$

References:

International Agency for Research on Cancer (IARC). 1982. IARC Monograph: Evaluation of the Carcinogenic Risk of Chemicals to Humans, Volume 29, WHO Publications Center, USA, Albany, NY, pp 1-416.

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U.S. Environmental Protection Agency (EPA). 1987. Integrated Risk Information System (IRIS database). Chemical file for benzene (CAS No. 71-43-2). Verification Date 10/9/87. Last Reviewed 10/9/87.

U.S. Environmental Protection Agency (EPA). 1980. Ambient Water Quality Criteria Document for Benzene. Washington, DC. EPA 440/5-80-018.

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GREAT LAKES WATER QUALITY INITIATIVE
TIER I HUMAN HEALTH CRITERIA FOR
CHLORDANE
CAS NO. 57-74-9

Tier 1 Human Noncancer Criterion

A review of the available literature indicates that the most appropriate study for HNC derivation for chlordane is a study conducted by Velsicol Chemical Corporation (1983a). In this study, 80 Fischer 344 rats of each sex were administered 0, 1, 5 or 25 ppm chlordane for 130 weeks. Hematological, biochemical, urinary and pathological measurements were made on eight animals/sex/group at weeks 26 and 52. The same measurements were made on animals which survived to week 130. Liver hypertrophy occurred in females at 5 ppm (0.273 mg/kg/d) and a NOEL of 1 ppm (0.055 mg/kg/d) was determined. No liver lesions were found in male rats and a NOEL of 25 ppm (0.1175 mg/kg/d) was determined.

The NOEL for female rats is slightly lower than the NOELs determined for mice and dogs. A 24-month chronic study in ICR mice found NOELs of 0.123 mg/kg and 0.138 mg/kg for male and female mice, respectively (Velsicol, 1983b). A study using Beagle dogs found NOELs of 0.06 mg/kg and 0.09 mg/kg for male and female dogs, respectively (Wazeter, 1967).

Data on the reproductive and developmental effects of chlordane are limited. ATSDR (1989) cited a study by Usami et al. (1986) which showed no malformations in pups whose dams were administered 20, 40 or 80 mg/kg/d chlordane from day 7 to 17 of gestation. The finding of this study suggests that exposure levels which may cause adverse effects on development are higher than the NOEL cited above for the Velsicol study (1983a). Other studies reported by Chernoff and Kavlock (1982) and Ingle (1952 as cited by EPA, 1990) also indicate that criteria derived from the chronic NOAEL of 0.055 mg/kg/d (Velsicol, 1983a) should be protective of potential developmental effects.

The quality of the Velsicol (1983a) rat study was deemed sufficient to derive a Tier 1 HNC. This study was also used by EPA (1989; 1990) to derive the oral RfD for chlordane. The HNC was derived from the female rat NOEL using an uncertainty factor of 1000 to account for interspecies variability (10) and intraspecies differences (10) and an additional uncertainty factor of 10 to account for the lack of an adequate reproduction study and adequate chronic study in a second mammalian species and the generally inadequate sensitive endpoints studied in existing studies.

$$ADE = \frac{NOAEL}{UF} = \frac{5.5 \times 10^{-2}\ mg/kg/d}{1000} = 5.5 \times 10^{-5}\ mg/kg/d$$

Where: Uncertainty Factor = 100, composed of:

10x for interspecies variability
10x for intraspecies differences
10x to account for lack of adequate reproduction study

Drinking Water Sources:

$$HNV = \frac{ADE \times BW \times RSC}{WC_d + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{5.5 \times 10^{-5} \text{ mg/kg/d} \times 70 \text{ kg} \times 0.8}{2 \text{ l/d} + [(0.0036 \times 116{,}600) + (0.0114 \times 154{,}200)]}$$

$$= 1.4 \times 10^{-3} \text{ ug/L}$$

Non-Drinking Water Sources:

$$HNV = \frac{ADE \times BW \times RSC}{WC_r + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{5.5 \times 10^{-5} \text{ mg/kg/d} \times 70 \text{ kg} \times 0.8}{0.01 \text{ l/d} + [(0.0036 \times 116{,}600) + (0.0114 \times 154{,}200)]}$$

$$= 1.4 \times 10^{-3} \text{ ug/L}$$

References:

Agency for Toxic Substances and Disease Registry (ATSDR). 1989. Toxicological Profile for Chlordane. Department of Health and Human Services. U.S. Public Health Service.

Chernoff, N. and R. J. Kavlock. 1982. An in vivo teratology screen utilizing pregnant mice. J. Toxicol. Environ. Hlth. 10:541-550.

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Velsicol Chemical Corporation. 1983a. Yonemura, T., F. Takamura and Y. Takahashi. Thirty-month chronic toxicity and tumorigenicity test in rats by chlordane technical. (Unpublished study by Research Institute for Animal Science in Biochemistry and Toxicology, Japan).

Velsicol Chemical Corporation. 1983b. Inui, S., K. Yamazaki, T. Yonemura, et al. Twenty-four month chronic toxicity and tumorigenicity test in mice by chlordane technical. (Unpublished study by Research Institute for Animal Science in Biochemistry and Toxicology, Japan).

Wazeter, F.X. 1967. Two-Year Chronic Feeding Study in the Beagle Dog. Sponsored by Velsicol Chemical Corporation (Unpublished).

Tier 1 Human Cancer Criterion

There are inadequate data available to determine whether chlordane is a human carcinogen (EPA, 1987; 1990). Chronic studies using four strains of mice (CD-1, B6C3F1, C5781/6N, ICR) of both sexes have shown an increase in the occurrence of liver tumors. Additional weight-of-evidence for chlordane's carcinogenicity is provided by its structural similarity to other compounds (i.e., dieldrin and heptachlor) which have been found to induce hepatocellular carcinomas in mice. The results of various mutagenicity studies are inconclusive as to this chemical's ability to cause mutagenic effects. The weight-of-evidence for chlordane carcinogenicity is sufficient for B2 (probable human carcinogen) classification (EPA, 1986; 1987; 1990). The data are sufficient to derive a Tier 1 HCC.

Two key studies (NCI, 1977; Velsicol, 1973 as cited in EPA, 1986) found a significant increase in hepatocellular carcinomas in treatment groups when compared to controls. Both studies also showed a dose-response relationship between exposure of mice to chlordane and the occurrence of liver tumors. EPA (1986; 1987; 1990) calculated four separate slope factors from these key studies, and derived a recommended slope factor of 1.3 $(mg/kg/d)^{-1}$ from the geometric mean of these slope factors. This method of computing a slope factor is used "in situations where no single study is judged most appropriate, yet several studies collectively support the estimate ..." (EPA, 1989). According to EPA (1989), the advantage of this method of determining the slope factor is that all relevant data are used in the computations.

$$RAD = \frac{\text{Risk Level}}{q1^*} = \frac{1 \times 10^{-5}}{1.3\ (mg/kg/d)^{-1}} = 7.69 \times 10^{-6}\ mg/kg/d$$

Drinking Water Sources:

$$HCV = \frac{RAD \times BW}{WC_d + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{7.69 \times 10^{-6} \text{ mg/kg/d} \times 70 \text{ kg}}{2 \text{ l/d} + [(0.0036 \times 116{,}600) + (0.0114 \times 154{,}200)]}$$

$$= 2.5 \times 10^{-4} \text{ ug/L}$$

Non-Drinking Water Sources:

$$HCV = \frac{RAD \times BW}{WC_r + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{7.69 \times 10^{-6} \text{ mg/kg/d} \times 70 \text{ kg}}{0.01 \text{ l/d} + [(0.0036 \times 116{,}600) + (0.0114 \times 154{,}200)]}$$

$$= 2.5 \times 10^{-4} \text{ ug/l}$$

References:

National Cancer Institute (NCI). 1977. Bioassay of Chlordane for possible carcinogenicity. NCI Carcinogenesis Tech. Rep. Ser. No. 8. U.S. DHEW Publ. No. (NIH) 77-808. Bethesda, MD.

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U.S. Environmental Protection Agency (EPA). 1990. Drinking Water Criteria Document for Heptachlor, Heptachlor Epoxide and Chlordane. Revised November, 1990. ECAO-CIN-406.

GREAT LAKES WATER QUALITY INITIATIVE
TIER 1 HUMAN HEALTH CRITERIA FOR
CHLOROBENZENE
CAS NO. 108-90-7

Tier 1 Human Noncancer Criterion

A review of the available literature indicates inadequate human data for quantitative risk assessment of chlorobenzene based on human health effects. Humans exposed occupationally to chlorobenzene intermittently for up to 2 years displayed signs of neurotoxicity including numbness, cyanosis (from depression of the respiratory center), hyperesthesia and muscle spasms (Rozenbaum, 1947, as cited in ATSDR, 1990). While these findings provide qualitative evidence that chlorobenzene is potentially neurotoxic, specific exposure levels are not available to support quantitative risk assessment.

Several animal studies were identified during a review of the available literature. The most appropriate basis for HNV derivation for chlorobenzene is the NOAEL from a subchronic dog study by Monsanto Company (1967). Young adult pure-bred beagle dogs (4/sex/group) were administered chlorobenzene in gelatin capsules, 5 days/week at doses of 0, 0.025, 0.050 and 0.250 ml/kg/day (converted per EPA (1989a) to 0, 27.25, 54.5 and 272.5 mg/kg/day, respectively) for 13 weeks. Four high-level dogs died or were sacrificed in moribund condition between the third and fourth weeks of the study. These deaths were preceded by anorexia, decreased activity, body weight loss, cachexia and coma. The four surviving high-level dogs exhibited temporary lack of appetite and body weight loss. Changes in hematology, clinical chemistry and urine analyses were observed at the high dose. Pathologic changes in the liver, kidney, gastrointestinal mucosa, and hematopoietic tissue were also observed in high-dose animals. At 54.5 mg/kg/day, slight hepatic alterations were observed, and severe cellular variations in the epithelium of the terminal proximal tubule in the kidney were also observed. The NOAEL and LOAEL for this study were 27.25 and 54.5 mg/kg/day, respectively.

The database is judged to be sufficient for Tier 1 HNC derivation. The key study (Monsanto, 1967) provides a subchronic NOAEL which is supported by the following additional data.

In a rat study performed by Monsanto Company and abstracted by Knapp et al. (1971), significant elevations were noted in liver and kidney weights of rats administered dietary levels of 100 and 250 mg/kg/day for 93 to 99 consecutive days. No remarkable histopathologic findings were reported. In addition, no effects were noted among rats receiving 12.5 or 50 mg/kg/day. The NOAEL and LOAEL for this study were 50 and 100 mg/kg/day, respectively (EPA, 1989a). The authors concluded that in comparison to rats, dogs displayed a greater sensitivity to chlorobenzene toxicity.

In a chronic study by the National Toxicology Program (NTP, 1985), groups of F344/N rats and B6C3F1 mice (50/sex/dose) were administered chlorobenzene by gavage in corn oil 5 days/week for 103 weeks. The male and female rats received 0, 60 or 120 mg/kg/day; the female mice received 0, 60 or 120 mg/kg/day and the male mice received 0, 30 or 60 mg/kg/day. A statistically significant decrease in the survival of high-dose male rats was observed. Histological examination of the liver showed hepatocellular necrosis, graded as minimal to mild, in all groups. In male mice, mortality at both dose levels was increased to a statistically significant level. No other chlorobenzene-related clinical toxicity was observed in mice.

Several reproductive and developmental studies have been performed with chlorobenzene. John et al. (1984) exposed Fischer 344 rats and New Zealand White rabbits by inhalation to chlorobenzene for 6 hours/day at doses of 0, 75, 210 or 590 ppm during periods of major organogenesis. Exposure to 590 ppm caused elevated liver weights in both species and decreased body weight gain and feed consumption in rats. The developmental NOAEL was 590 ppm for both species (equivalent to 216 mg/kg/day for rats and 125 mg/kg/day for rabbits, as per EPA, 1989a). The maternal NOAELs were 210 ppm (equivalent to 77 mg/kg/day, as per EPA, 1989a) for rats and 75 ppm (equivalent to 16 mg/kg/day, as per EPA, 1989a) for rabbits.

In a two-generation reproduction inhalation study in rats (Nair et al., 1987) groups of 30 male and 30 female Sprague-Dawley CD rats (F_0 generation) were exposed to chlorobenzene at target concentrations of 0, 50, 150 or 450 ppm for 10 weeks prior to mating and during mating, gestation, and lactation. Groups of 30 male and 30 female F_1 animals were exposed to the same concentrations of chlorobenzene as the F_0 parents, initiated 1 week postweaning and lasting through mating, gestation and lactation. Hepatocellular hypertrophy and renal changes were observed among F_0 and F_1 male rats exposed to 150 and 450 ppm but exposure of rats to chlorobenzene at levels of 50, 150 or 450 ppm did not have any adverse effects on reproductive performance or fertility of male and female rats. A reproductive NOAEL of 165 mg/kg/day and a systemic NOAEL of 18 mg/kg/day (conversions were from EPA, 1989a) were determined from this study.

The HNV is derived from the NOAEL dose of 27.25 mg/kg/day (converted to 19.46 mg/kg/day for 5 days/week administration) from the 13-week dog study by Monsanto Company (1967) with an uncertainty factor of 1000. Data from other studies (John et al., 1984; Nair et al., 1987) suggest that this value will be protective of reproductive/developmental effects. This approach is consistent with the risk assessment of chlorobenzene for the derivation of the oral RfD, drinking water equivalent level (DWEL), and maximum contaminant level goal (MCLG) by EPA (EPA,1989a; EPA, 1989b; EPA, 1989c).

$$ADE = \frac{NOAEL}{UF} = \frac{19.46\ mg/kg/d}{1000} = 1.946 \times 10^{-2}\ mg/kg/d$$

Where: Uncertainty Factor = 1000, composed of:
10x for interspecies variability
10x for intraspecies differences
10x for subchronic exposure duration

Drinking Water Sources:

$$HNV = \frac{ADE \times BW \times RSC}{WC_d + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{1.946 \times 10^{-2}\ mg/kg/d \times 70\ kg \times 0.8}{2\ l/d + [(0.0036 \times 15) + (0.0114 \times 24)]}$$

$$= 4.7 \times 10^{2}\ ug/L$$

Non-Drinking Water Sources:

$$HNV = \frac{ADE \times BW \times RSC}{WC_r + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{1.946 \times 10^{-2}\ mg/kg/d \times 70\ kg \times 0.8}{0.01\ l/d + [(0.0036 \times 15) + (0.0114 \times 24)]}$$

$$= 3.2 \times 10^{3}\ ug/L$$

References:

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Tier 1 Human Cancer Criterion

Chlorobenzene is not considered carcinogenic.

GREAT LAKES WATER QUALITY INITIATIVE
TIER 1 HUMAN HEALTH CRITERIA FOR
CYANIDES
CAS NO. 57-12-5

Tier 1 Human Noncancer Criterion

A review of the available literature indicates inadequate human data for quantitative risk assessment of cyanides based on human health effects. Qualitative data suggest that chronic dietary exposure to naturally occurring cyanogens in cassava results in thyroid abnormalities in African countries where cassava is a staple crop. Effects seen, including endemic goiter, cretinism and congenital hypothyroidism, were potentiated by low iodine intake and other dietary deficiencies. Tropical ataxic neuropathy has also been linked to chronic cyanide ingestion from cassava derivatives (Njoh, 1990). However, these data do not provide a dose-response relationship (EPA, 1985a; 1985b; ATSDR, 1988; Njoh, 1990).

From animal studies on the chronic oral toxicity of inorganic salts of cyanide, the most appropriate basis for HNV derivation for cyanides is the NOAEL from the chronic rat feeding study of Howard and Hanzal (1955). Weanling rats (10/sex/group) were offered food fumigated with hydrogen cyanide at dietary concentrations of 100 and 300 ppm HCN, averaging 73 and 183 mg CN^-/kg diet) for two years. Dose levels were approximately 4.6 or 10.8 mg CN^-/kg bw/day to females, and 3.6 or 7.5 mg CN^-/kg bw/day to males (EPA, 1985b, 1990). At termination, hematological values were within normal limits and neither gross nor microscopic examination of tissues (including thyroid) revealed evidence of pathology due to exposure in any of the exposure groups. Therefore, the NOAEL from this study is 10.8 mg CN^-/kg bw/day.

The database is judged to be sufficient for Tier 1 HNC derivation. The key study (Howard and Hanzal, 1955) provides a chronic NOAEL which is supported and supplemented by other data.

In a chronic study (Philbrick et al., 1979), ten male weanling rats were given 1500 ppm potassium cyanide in the diet for 11.5 months. The administered dose was approximately 75 mg KCN/kg bw/day, or 30 mg CN^-/kg bw/day (ATSDR, 1988; EPA, 1985a; 1985b). The cyanide exposure in rats receiving either normal or restricted diet resulted in reduced body weight gain, decreased thyroid gland activity and increased thyroid weights.

In a study by Tewe and Maner (1981b), pregnant Yorkshire pigs (6/dose group) were fed fresh cassava diets containing 0, 276 or 521 mg cyanide (added as KCN) per kg of fresh cassava offered during gestation and parturition. On the 110th day of gestation, two gilts per dose group were sacrificed and the fetuses were evaluated. The remaining gilts in each dose group were allowed to naturally deliver and were then maintained on a

diet with no cyanide throughout the 56-day lactation period. No serious interference was observed with the production of the first litter of offspring by gilts receiving cassava diets containing up to 521 ppm added cyanide during gestation. Gilts in the high dose group, exhibited possible adverse effects on the thyroid (increased weight) and kidney (proliferation of glomerular cells). The high exposure level also suggests a LOAEL for developmental effects, as the 110-day-old fetuses had decreased relative spleen, thyroid and heart weights. The evidence that the thyroid may be a sensitive target organ in pigs lends support to the thyroid effects reported by Jackson (1988; see later discussion). However, data interpretation is difficult due to the small number of gilts evaluated (2/dose group). The administered levels of 276 and 521 ppm CN^- in the diet convert to 7.7 and 17 mg CN^-/kg bw/day for the gilts, using the reported animal body weights and food intake from the study. The NOAEL for this study was 276 ppm CN^- in the diet, or approximately 7.7 mg CN^-/kg bw/day.

Another developmental study (Tewe and Maner, 1981a) reports that 500 ppm KCN administered in the diet to rats resulted in a decreased protein efficiency ratio among offspring during the postweaning growth phase. The dose level has been converted to approximately 50 mg CN^-/kg/day assuming a 10% food conversion factor (ATSDR, 1988), or approximately 10.6 mg CN^-/kg/day per EPA (1985b).

Other available oral studies are more limited in design, including the only relevant study with drinking water exposure. Palmer and Olson (1979) gave 7 male Sprague-Dawley rats 200 mg/l KCN in water (or 80 mg/l CN^-; 10 mg CN^-/kg/day per EPA, 1985a) or 200 ppm KCN in diet (80 mg CN^-/kg food; 8 mg CN^-/kg/day per EPA, 1985a) for 21 days. At the end of the study, the only parameters evaluated were body weight and liver weight. Liver weights were increased over controls following drinking water exposure only. Although inadequate for criteria derivation, this study suggests that cyanide via drinking water is more potent for inducing effects than feeding studies, but is less potent than gavage exposures.

In another noteworthy but limited study, the effects of oral cyanide on glucose metabolism, thyroid function and an array of behavioral indices were evaluated in miniature pigs (Jackson, 1988). Three swine/dose group (mixed sexes) received 0, 0.4, 0.7 or 1.2 mg CN^-/kg/day by intraoral bolus as KCN in aqueous solution, daily for 24 weeks. The author reports that treatment resulted in a dose-related increase in the fasting blood glucose level, dose-related decreases in T_3 and T_4 thyroid hormones, and numerous altered behaviors. By Chi-square analyses these changes were determined to be significant, even in the low exposure group with regard to some parameters. The alterations noted were more pronounced in the high-dose group, particularly for thyroid hormone levels, the parameter most clearly indicative of adverse effects. Suppression of T_3 and T_4 was dose-related with a much

stronger response in the high-dose group (roughly double the effect seen in the mid-dose group at 24 weeks). However, the limitations of the study design and reporting are substantial (Papa, 1990, personal communication). Some of the most critical deficiencies in design or reporting include: small animal numbers per group; lack of body weight and organ weight data; exposure pattern as a single daily bolus dose; unclear biological significance of the reported biochemical effects; no report of the variance about the mean for T_3, T_4, and blood glucose values; and the distribution of sexes among the four groups was not reported. The latter point appears critical because from the 12 animals distributed evenly among the four groups, five were females, and seven were castrated males. The castrated males were, therefore, unevenly represented among the groups and the castration effect on thyroid levels and behavior is likely to be significant (Papa, 1990, personal communication).

The 2-year dietary exposure study by Howard and Hanzal (1955) has been selected as the key study for the derivation of the risk assessment of cyanide in drinking water by EPA (1985a, 1985b, 1990). Those assessments have applied an additional uncertainty factor of 5 due to the dietary method of exposure. This is intended to account for the relative tolerance to cyanide when it is ingested with food rather than when it is ingested in drinking water. The value of 5 was based on an evaluation of cyanide-binding affinity of food and the GI absorption of cyanide in food versus drinking water by Dr. Ernest Foulkes of the University of Cincinnati who served as an external reviewer for EPA (1985a) (Papa, 1990, personal communication). This 5-fold (or 20%) adjustment factor for differential bioavailability between cyanide in feed and in drinking water is concluded to be appropriate and scientifically supportable in a more recent analysis (Pearsall and Chrostowski, 1990).

The HNC is therefore derived from the HNOAEL dose of 10.8 mg CN^-/kg/day in rats via feed (Howard and Hanzal, 1955), and an uncertainty factor of 500.

$$ADE = \frac{NOAEL}{UF} = \frac{10.8 \text{ mg } CN^-/kg/d}{500} = 2.16 \times 10^{-2} \text{ mg/kg/d}$$

Where: Uncertainty Factor = 500, composed of:
- 10x for interspecies variability
- 10x for intraspecies differences
- 5x adjustment for bioavailability, feed vs. drinking water

Drinking Water Sources:

$$HNV = \frac{ADE \times BW \times RSC}{WC_d + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{2.16 \times 10^{-2} \text{ mg/kg/d} \times 70 \text{ kg} \times 0.8}{2 \text{ l/d} + [(0.0036 \times 1) + (0.0114 \times 1)]}$$

$$= 6.0 \times 10^{2} \text{ ug/L}$$

Non-Drinking Water Sources:

$$\text{HNV} = \frac{\text{ADE} \times \text{BW} \times \text{RSC}}{WC_r + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{2.16 \times 10^{-2} \text{ mg/kg/d} \times 70 \text{ kg} \times 0.8}{0.01 \text{ l/d} + [(0.0036 \times 1) + (0.0114 \times 1)]}$$

$$= 4.8 \times 10^{4} \text{ ug/L}$$

Note: BAF = 1 by default.

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Tier 1 Human Cancer Criterion

Cyanides are not considered carcinogenic.

GREAT LAKES WATER QUALITY INITIATIVE
TIER I HUMAN HEALTH CRITERIA FOR
P,P'-DICHLORODIPHENYLTRICHLOROETHANE (DDT)
CAS NO. 50-29-3

Tier 1 Human Noncancer Criterion

A review of the available literature indicates that the most appropriate basis for HNC derivation for DDT is the NOAEL from the subchronic rat feeding study of Laug et al. (1950). Weanling rats (15/sex/group) were fed commercial-grade DDT (81% p,p'-DDT, 19% o,p'-DDT) at levels of 0, 1, 5, 10 or 50 ppm for 15-27 weeks. The critical toxic effect was liver toxicity, demonstrated as relatively mild dose-dependent histopathologic changes in hepatocytes at doses of 5 ppm and higher. These included hepatocellular hypertrophy, increased cytoplasmic oxyphilia, and peripheral basophilic cytoplasmic granules. The NOEL was 1 ppm, or 0.05 mg/kg bw/day assuming a food consumption rate of 5% body weight per day. The LOAEL was 5 ppm (0.25 mg/kg bw/day).

The database is judged to be sufficient for Tier 1 HNC derivation. The key study (Laug et al., 1950) provides a subchronic (greater than 90 day) NOEL which is supported and supplemented by other data. In a 2-year rat dietary exposure study (Fitzhugh, 1948) rats were exposed to 10-800 ppm DDT in feed, resulting in liver lesions at all dose levels with a LOAEL of 10 ppm (0.5 mg/kg bw/day). The available mammalian reproduction and developmental studies of DDT indicate that an HNC derived from the critical effect of liver toxicity will be protective of potential human reproductive/ developmental effects (EPA, 1985). The HNC is based on the subchronic rat NOEL of 0.05 mg/kg bw/day, with a total uncertainty factor of 100. An uncertainty factor for subchronic exposure duration is not included because of the corroborating chronic study in the database. This approach is consistent with the oral RfD development by EPA (1985).

$$ADE = \frac{NOAEL}{UF} = \frac{0.05\ mg/kg/d}{100} = 5.0 \times 10^{-4}\ mg/kg/d$$

Where: Uncertainty Factor = 100, composed of:
10x for interspecies variability
10x for intraspecies differences

Drinking Water Sources:

$$HNV = \frac{ADE \times BW \times RSC}{WC_d + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{5 \times 10^{-4} \text{ mg/kg/d} \times 70 \text{ kg} \times 0.8}{2 \text{ l/d} + [(0.0036 \times 376{,}400) + (0.0114 \times 1{,}114{,}000)]}$$

$$= 2.0 \times 10^{-3} \text{ ug/L}$$

Non-Drinking Water Sources:

$$HNV = \frac{ADE \times BW \times RSC}{WC_r + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{5 \times 10^{-4} \text{ mg/kg/d} \times 70 \text{ kg} \times 0.8}{0.01 \text{ l/d} + [(0.0036 \times 376{,}400) + (0.0114 \times 1{,}114{,}000)]}$$

$$= 2.0 \times 10^{-3} \text{ ug/L}$$

References:

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Laug, E., A. Nelson, O. Fitzhugh and F. Kunze. 1950. Liver cell alteration and DDT storage in the fat of the rat induced by dietary levels of 1-50 ppm DDT. J. Pharmacol. Exp. Therap. 98:268-273.

U.S. Environmental Protection Agency (EPA). 1985. Integrated Risk Information System (IRIS). Chemical file for DDT (50-29-3). Verification Date 12/18/85. Last Revised 9/30/87.

Tier 1 Human Cancer Criterion

A review of the available literature for DDT carcinogenicity reveals a lack of adequate epidemiological data and an extensive database of chronic oral rodent bioassays. These studies indicate that the induction of liver tumors is the most consistent and significant tumorigenic response to DDT in rodents. EPA (1987) has classified the weight of evidence of DDT carcinogenicity as B2 based on multiple positive studies in two species (mice and rats), with ancillary evidence including promoting activity, genotoxicity, and structural relation to other rodent liver carcinogens. Therefore, the data are sufficient for Tier 1 HCC derivation.

The animal bioassay providing the highest slope factor estimation is the multigeneration mouse feeding study of Tarjan and Kemeny (1969). The predominant tumor types were leukemias and lung tumors; a significant liver response was not seen. EPA (1980) derived ambient water quality criteria from the slope factor of 8.422 $(\text{mg/kg/day})^{-1}$ from this study.

EPA (1986a) evaluated the carcinogenicity of DDT and other related compounds and determined that the Tarjan and Kemeny

(1969) study was not the most appropriate basis for quantitative risk assessment. The study's findings were not consistent with the numerous other positive bioassays in terms of the organ site (lung/leukemia versus liver) and the slope factor (about an order of magnitude greater). This slope factor was judged to be a statistical outlier in relation to the liver tumor induction data from six key studies, and the quality and validity of the study was also questionable. EPA (1986a) derived a slope factor from the consistent finding of liver tumor induction in rats and mice, for which the six key studies provided slope factors within a 13-fold range. The recommended slope factor of 3.4 E-1 $(mg/kg/day)^{-1}$ was derived as the geometric mean of ten slope factors from those six studies (Turusov et al., 1973; Terracini et al., 1973; Thorpe and Walker, 1973; Tomatis and Turusov, 1975; Cabral et al., 1982; Rossi et al., 1977). The averaging procedure was followed because no further database refinement or rejection could be logically made, and the geometric average of the values was viewed as the best rational estimate of the slope factor (EPA, 1986a). The EPA's CRAVE workgroup has reviewed and accepted this approach to slope factor estimation as a method to include all relevant data (EPA, 1987).

This averaging approach to slope factor estimation utilizing multiple studies, species, strains and sexes has not generally been recommended in earlier EPA guidelines (EPA, 1980; 1986b). However, more recently, EPA (1989) has stated: "Occasionally, in situations where no single study is judged most appropriate, yet several studies collectively support the estimate, the geometric mean of estimates from all studies may be adopted as the slope. This practice insures the inclusion of all relevant data" (EPA, 1989). In the specific case of DDT, the averaging process as applied to the best available studies may be the most reasonable means of quantitatively characterizing the carcinogenicity of DDT (Schoeny, 1991; Holder, 1991; Bayard, 1991).

The Tier 1 Human Cancer Criteria for DDT are derived from the slope factor of 3.4×10^{-1} $(mg/kg/d)^{-1}$ based on rodent liver tumor induction in the six key studies.

$$RAD = \frac{\text{Risk Level}}{q1^*} = \frac{1 \times 10^{-5}}{3.4 \times 10^{-1}\ (mg/kg/d)^{-1}}$$

$$= 2.94 \times 10^{-5}\ mg/kg/d$$

Drinking Water Sources:

$$HCV = \frac{RAD \times BW}{WC_d + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{2.94 \times 10^{-5}\ mg/kg/d \times 70\ kg}{2\ l/d + [(0.0036 \times 376{,}400) + (0.0114 \times 1{,}114{,}000)]}$$

$$= 1.5 \times 10^{-4}\ ug/L$$

Non-Drinking Water Sources:

$$HCV = \frac{RAD \times BW}{WC_r + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{2.94 \times 10^{-5}\ mg/kg/d \times 70\ kg}{0.01\ l/d + [(0.0036 \times 376{,}400) + (0.0114 \times 1{,}114{,}000)]}$$

$$= 1.5 \times 10^{-4}\ ug/L$$

References:

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U.S. Environmental Protection Agency (EPA). 1980. 45 Federal Register No. 231, pp. 79347-79356. Appendix C - Guidelines and Methodology Used in the Preparation of the Consent Decree Water Criteria Documents.

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U.S. Environmental Protection Agency (EPA). 1986b. 51 Federal Register No. 185, pp. 33992-34003. Guidelines for Carcinogen Risk Assessment.

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GREAT LAKES WATER QUALITY INITIATIVE
TIER 1 HUMAN HEALTH CRITERIA FOR
DIELDRIN
CAS NO. 60-57-1

Tier 1 Human Noncancer Criterion

A review of the available literature indicates that the most appropriate study for HNC derivation for dieldrin is a two year study conducted by Walker et al. (1969). In this study, 25 Carworth Farm "E" rats of each sex were administered 0.1, 1.0 or 10.0 ppm dieldrin in their diet and 45 rats of each sex were used as controls. At the end of two years, the females exposed to 1.0 and 10.0 ppm had increased liver weights and liver-to-body weight ratios. Histopathological examination of these animals found changes in perenchymal cells which included focal proliferation and focal hyperplasia. A NOAEL of 0.1 ppm (estimated to be 0.005 mg/kg/day) was determined from the study. In support of this value a systemic NOEL of 0.005 mg/kg/day was calculated for dogs in the same study.

Studies examining the reproductive effects of dieldrin are lacking (EPA, 1987). A review of studies which examine the developmental effects of dieldrin in mice (Chernoff et al., 1975; Dix et al., 1977) and rats (Harr et al., 1970; Chernoff et al., 1975) suggest that exposure levels which may result in adverse developmental effects are higher than the NOAEL determined in the Walker et al. (1969) study.

The quality of the Walker et al. (1969) study was deemed sufficient to derive a Tier 1 HNC. This study was also used by EPA (1987) to derive the oral RfD for dieldrin. The HNC was derived from the NOAEL (0.005 mg/kg/day) using an uncertainty factor of 100 to account for interspecies variability and intraspecies differences.

$$ADE = \frac{NOAEL}{UF} = \frac{0.005\ mg/kg/d}{100} = 5.0 \times 10^{-5}\ mg/kg/d$$

Where: Uncertainty Factor = 100, composed of:
10x for interspecies variability
10x for intraspecies differences

Drinking Water Sources:

$$HNV = \frac{ADE \times BW \times RSC}{WC_d + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{5.0 \times 10^{-5}\ mg/kg/d \times 70\ kg \times 0.8}{2\ l/d + [(0.0036 \times 72{,}610) + (0.0114 \times 571{,}000)]}$$

$$= 4.1 \times 10^{-4}\ ug/L$$

Non-Drinking Water Sources:

$$HNV = \frac{ADE \times BW \times RSC}{WC_r + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{5.0 \times 10^{-5} \text{ mg/kg/d} \times 70 \text{ kg} \times 0.8}{0.01 \text{ l/d} + [(0.0036 \times 72{,}610) + (0.0114 \times 571{,}000)]}$$

$$= 4.1 \times 10^{-4} \text{ ug/L}$$

References:

Chernoff, N., R.J. Kavlock, J.R. Kathrein, J.M. Dunn and J.K. Haseman. 1975. Prenatal effects of dieldrin and photo-dieldrin in mice and rats. Toxicol. Appl. Pharmacol. 31:302-308.

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Tier 1 Human Cancer Criterion

According to EPA (1987a), there are inadequate data available to ascertain whether dieldrin is a human carcinogen. However, chronic studies have shown that dieldrin induces the formation of liver tumors in seven strains of mice when administered orally. Additional support for dieldrin's carcinogenicity is provided by its structural similarity to other compounds (i.e. heptachlor and chlordane) which have been found to induce tumors in rodents. Dieldrin has also produced a positive response in several mutagenicity studies. The weight-of-evidence for dieldrin carcinogenicity is sufficient for B2 (probable human carcinogen) classification (EPA, 1987a). The data are sufficient to derive a Tier 1 HCC.

Six key studies (Davis, 1965 as reevaluated by Reuber and cited in Epstein, 1975; Walker et al., 1972; Thorpe and Walker,

1973; NCI, 1978; Tennekes et al., 1981; Meierhenry et al., 1983) have reported liver tumor induction in mice exposed orally to dieldrin. EPA (1987a; 1987b) calculated 13 different slope factors using data from these studies. The calculated slope factors were within an eight-fold range. EPA (1987a; 1987b) calculated a single oral slope factor of 1.6×10^{1} $(mg/kg/day)^{-1}$ by taking the geometric mean of the 13 slope factors computed from the key studies. This method of computing a slope factor is used "in situations where no single study is judged most appropriate, yet several studies collectively support the estimate..." (EPA, 1989). According to EPA (1989), the advantage of this method of determining the slope factor is that all relevant data are used in the computation.

$$RAD = \frac{\text{Risk Level}}{q1^*} = \frac{1 \times 10^{-5}}{1.6 \times 10^{1}\ (mg/kg/d)^{-1}}$$

$$= 6.25 \times 10^{-7}\ mg/kg/d$$

Drinking Water Sources:

$$HCV = \frac{RAD \times BW}{WC_d + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{6.25 \times 10^{-7}\ mg/kg/d \times 70\ kg}{2\ l/d + [(0.0036 \times 72{,}610) + (0.0114 \times 571{,}000)]}$$

$$= 6.5 \times 10^{-6}\ ug/L$$

Non-Drinking Water Sources:

$$HCV = \frac{RAD \times BW}{WC_r + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{6.25 \times 10^{-7}\ mg/kg/d \times 70\ kg}{0.01\ l/d + [(0.0036 \times 72{,}610) + (0.0114 \times 571{,}000)]}$$

$$= 6.5 \times 10^{-6}\ ug/L$$

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GREAT LAKES WATER QUALITY INITIATIVE
TIER 1 HUMAN HEALTH CRITERIA FOR
2,4-DIMETHYLPHENOL
CAS NO. 105-67-9

Tier 1 Human Noncancer Criterion

A review of the available literature indicates that HNV derivation for 2,4-dimethylphenol (2,4-DMP) is most appropriately based on the subchronic oral mouse study conducted by EPA (1989). Groups consisting of 30 male and 30 female albino mice were administered 2,4-DMP by gavage at dose levels of 0, 5, 50 or 250 mg/kg/day for 90 days. At day 30, an interim sacrifice was performed on at least 8 males and 9 females from each group. Effects examined included mortality, clinical signs, body weights, food consumption, ophthalmology, hematology, clinical chemistry, organ weights, and gross histopathology. Toxicologically relevant clinical signs observed only after week 6 at 250 mg/kg/day in both sexes included squinting, lethargy, prostration, and ataxia, with onset shortly after dosing. Statistically significant lower mean corpuscular volume and mean corpuscular hemoglobin concentrations were observed in female mice at 250 mg/kg/day during the final but not during the interim sacrifice. At interim sacrifice, the blood urea nitrogen (BUN) levels for females at 50 and 250 mg/kg/day were significantly lower than the vehicle controls, while at the final sacrifice, the BUN levels for females at 50 mg/kg/day were significantly higher than the vehicle control group. For only the low-dose (5 mg/kg/day) males at the interim sacrifice, cholesterol levels were significantly higher than the vehicle control group. Increased adrenal weights were observed in low-dose (5 mg/kg/day) but not mid- to high-dose females when compared to vehicle control animals. Since the reported changes in BUN, serum cholesterol and adrenal weights were not dose- or time-dependent, they may be interpreted to be spurious findings. The NOAEL and LOAEL for this study were 50 and 250 mg/kg/day, respectively, based on clinical signs and hematological changes.

The database is judged to be sufficient for Tier 1 HNC derivation because the key study (EPA, 1989) provides a subchronic NOAEL. However, there is a paucity of supplemental and supportive data. No useful chronic, reproductive or developmental studies are available. The overall findings from the 90-day study (EPA, 1989) compare favorably with the results of a 14-day mice gavage study (EPA, 1987; as cited in EPA, 1989; EPA, 1990) conducted at the same laboratory. In the 14-day study, the only toxicological signs observed in males and females administered 250 mg/kg/day were lethargy, prostration, and ataxia. This is the same dose at which critical effects were found in the 90-day study (EPA, 1989).

The HNV is derived from the NOAEL dose of 50 mg/kg/day from the 90-day gavage mouse study by EPA (1989) with an uncertainty

factor of 3000. This approach is consistent with the derivation of the oral RfD for 2,4-DMP by EPA (1990).

$$ADE = \frac{NOAEL}{UF} = \frac{50\ mg/kg/d}{3000} = 1.67 \times 10^{-2}\ mg/kg/d$$

Where: Uncertainty Factor = 3000, composed of:
- 10x for interspecies variability
- 10x for intraspecies differences
- 10x for subchronic exposure duration
- 3x for substantial gaps in the database

Drinking Water Sources:

$$HNV = \frac{ADE \times BW \times RSC}{WC_d + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{1.67 \times 10^{-2}\ mg/kg/d \times 70\ kg \times 0.8}{2\ l/d + [(0.0036 \times 5) + (0.0114 \times 7)]}$$

$$= 4.5 \times 10^{2}\ ug/L$$

Non-Drinking Water Sources:

$$HNV = \frac{ADE \times BW \times RSC}{WC_r + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{1.67 \times 10^{-2}\ mg/kg/d \times 70\ kg \times 0.8}{0.01\ l/d + [(0.0036 \times 5) + (0.0114 \times 7)]}$$

$$= 8.7 \times 10^{3}\ ug/L$$

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U.S. Environmental Protection Agency (EPA). 1987. Fourteen-Day Gavage Study in Albino Mice Using 2,4-Dimethylphenol. Study No. 410-2830, prepared by Dynamac Corporation, Rockville, MD, for the Office of Solid Waste and Emergency Response, Washington, DC. As cited in EPA (1989, 1990).

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Tier 1 Human Cancer Criterion

2,4-Dimethylphenol is not considered carcinogenic.

GREAT LAKES WATER QUALITY INITIATIVE
TIER 1 HUMAN HEALTH CRITERIA FOR
2,4-DINITROPHENOL
CAS NO. 51-28-5

Tier 1 Human Noncancer Criterion

A review of the available literature on the toxic effects and therapeutic use of 2,4-dinitrophenol (2,4-DNP) indicates that the HNC derivation is most appropriately based upon the human dose-response following exposure to 2,4-DNP as reviewed by Horner (1942).

Numerous studies on 2,4-DNP and its toxic effects on humans are available (Horner, 1942; SRC, 1981). Commonly-reported toxic effects included gastrointestinal disturbances (nausea, vomiting, loss of appetite), cutaneous rashes, neuritis, agranulocytosis of the bone marrow, and jaundice. Liver and kidney and cardiovascular damage was rarely reported. Evidence of cardiovascular effects was limited to abnormal electrocardiograms indicating functional abnormalities of the heart, although fragmentation of the heart muscle was reported in cases of fatal poisoning. Nine cases of mortality resulting from 2,4-DNP poisoning were cited. Death usually occurred within 24 hours after the onset of such toxic manifestations as dizziness, fatigue, dyspnea, high temperature, intense thirst, and excessive perspiration.

In the study by Horner (1942), bilateral cataract formation was frequently observed in patients receiving 2,4-DNP as a weight-loss agent. The study reported that cataracts developed in more than 164 persons after the use of dinitrophenol, an estimated incidence of 0.86 percent. The study did not include a control group, however the researcher noted that this type of cataract is not expected to occur in some of the age groups which exhibited cataracts in the study. Formation of cataracts occurred either during dosing or within several months to a year after the final dose was taken. Cataracts were observed in patients receiving as little as 2 mg/kg bw/day which was the lower range of the recommended therapeutic dose for obesity. This LOAEL determined from the Horner (1942) study was deemed sufficient for the derivation of a Tier 1 HNC.

In a 6-month feeding study, male rats (from the Breeding and Laboratory Institute, Brooklyn, NY) were administered 2,4-DNP at dietary levels of 0, 100, 200, 500 and 1000 ppm for 178-179 days (Spencer et al., 1948). There were 14, 12, 12, 9 and 14 rats per dietary level, respectively. An additional 10 rats were fed 2000 ppm but after 24 days this group experienced 40% mortality and the remaining animals at 2000 ppm were sacrificed and examined at this time. These animals were emaciated and had empty gastrointestinal tracts, enlarged spleens with hemosiderosis, testicular atrophy, and increased levels of blood urea nitrogen. Rats fed 1000 ppm 2,4-DNP suffered a reduction in body weight

gain of 10-15%, a slight depletion of body fat, a very slight increase in the average weight of the kidneys, and a very slight decrease in the weight of the heart. Blood urea nitrogen levels were elevated in 2/14 animals at 1000 ppm. Reduced growth occurred at 500 ppm and a significant increase (between 91% and 92% above controls) in kidney weights occurred at all dietary concentrations. The authors concluded that the male rats maintained for six months on diets containing 200 ppm (and presumably 100 ppm) showed no appreciable ill effects. However, because there was a statistically significant increase in kidney weights at all dietary concentrations, the dose of 100 ppm may be considered the LOAEL for this study. Using a food consumption value of 0.08 kg/kg bw (EPA, 1988), the LOAEL for the Spencer et al. (1948) study was 8 mg/kg bw/day. This is very close to the LOAEL of 2.0 mg/kg bw/day which was calculated using the human data from Horner (1942). EPA (1980) derived an Acceptable Daily Intake (ADI) from an estimated NOAEL of 5.4 mg/kg/day (100 ppm group) from the study by Spencer et al. (1948).

In a teratology study with 2,4-DNP, Gibson (1973) reported that neither intraperitoneal (7.7 and 13.6 mg/kg/day) nor oral (25.5 and 38.2 mg/kg/day) doses of 2,4-DNP administered to pregnant Swiss-Webster mice during early organogenesis (days 10-12 of gestation) produced morphological defects. However, the higher intraperitoneal dose was embryotoxic and the higher intraperitoneal and oral doses produced overt signs of toxicity (hyperexcitability and hyperthermia) in the dams.

The HNV is derived from the LOAEL (2.0 mg/kg bw/day) determined from the human data summarized by Horner (1942) using an uncertainty factor of 1000. This approach is consistent with the derivation of the oral RfD for 2,4-DNP by EPA (1986).

$$ADE = \frac{NOAEL}{UF} = \frac{2\ mg/kg/d}{1000} = 2.0 \times 10^{-3}\ mg/kg/d$$

Where: Uncertainty Factor = 1000, composed of:
- 10x for interspecies variability
- 10x for intraspecies differences
- 10x for subchronic exposure duration

Drinking Water Sources:

$$HNV = \frac{ADE \times BW \times RSC}{WC_d + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{2.0 \times 10^{-3}\ mg/kg/d \times 70\ kg \times 0.8}{2\ l/d + [(0.0036 \times 2) + (0.0114 \times 2)]}$$

$$= 55\ ug/L$$

Non-Drinking Water Sources:

$$HNV = \frac{ADE \times BW \times RSC}{WC_r + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{2.0 \times 10^{-3}\ mg/kg/d \times 70\ kg \times 0.8}{0.01\ l/d + [(0.0036 \times 2) + (0.0114 \times 2)]}$$

$$= 2.8 \times 10^{3}\ ug/L$$

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Tier 1 Human Cancer Criterion

2,4-Dinitrophenol is not considered carcinogenic.

GREAT LAKES WATER QUALITY INITIATIVE
TIER 1 HUMAN HEALTH CRITERIA FOR
HEXACHLOROBENZENE
CAS NO. 118-74-1

Tier 1 Human Noncancer Criteria

A review of the available information on hexachlorobenzene (HCB) toxicity, including reviews by EPA (1980; 1985a; 1985b; 1988), indicates that the database is sufficient for Tier 1 HNC derivation. The best available data consist of laboratory animal studies.

The principle human data on HCB toxicity consist of widespread toxic effects among several thousand Turkish citizens exposed to HCB via consumption of fungicide-treated grain during 1955-1959. The resulting effects included porphyria cutanea tarda (PCT), neurotoxicity, liver damage, and increased infant mortality. The exposure has been estimated at 50-200 mg/day over an extended period, without further description of the dosage estimation method (Cam and Nigogosyan, 1963). The human data cannot be used for quantitative risk assessment because accurate exposure data are not available (EPA, 1988).

The available literature indicates that HCB is a potent developmental toxicant in several animal species. Kitchin et al. (1982) exposed rats to 0, 60, 80, 100, 120 and 140 ppm HCB in feed (doses ranged from 0 to 10 mg/kg/day). They reported a dose-dependent increase in mortality of pups in the $F1_a$ and $F1_b$ litters. Grant et al. (1977) conducted a 4-generation reproduction study with rats at food HCB levels in the diet of 0, 10, 20, 40, 80, 160, 320 and 640 ppm. They concluded that 20 ppm (about 1.5 mg/kg/day) was a NOAEL, while 40 ppm (about 3 mg/kg/day) resulted in increased liver weights in weanlings.

Rush et al. (1983) exposed mink to 0, 1 or 5 ppm in feed (about 0.16 or 0.78 mg/kg/day), resulting in profound effects on kit survivability to weaning at the high dose. Mortality was 8.2 percent, 4.1 percent and 77.4 percent among controls, low dose, and high dose groups, respectively. Bleavins et al. (1984a, 1984b) also reported that mink, as well as ferrets, are highly sensitive to the developmental effects of HCB. Mink were found to be more sensitive than ferrets, while both appeared more sensitive than rats according to published data. The most profound effects reported were decreased mink birth weights at adult dietary levels as low as 1 ppm and a dose-related increase in kit mortality at three weeks of age among both mink and ferrets at levels as low as 1 ppm (about 0.14 and 0.11 mg/kg/day for mink and ferrets, respectively). Additionally, effects were seen on the levels of hypothalamic dopamine of mink kits and on hypothalamic serotonin in adult mink. These changes were statistically significant at levels as low as 1 ppm in feed. A NOAEL was not reported.

Arnold et al. (1985) exposed male and female rats to dietary HCB levels of 0, 0.32, 1.6, 8.0 or 40 ppm for 90 days prior to mating and until 21 days after parturition (at weaning). The offspring were exposed in utero, from maternal nursing, and from their diets for the remainder of their lifetime. The total study period was 130 weeks. A NOAEL was reported at 1.6 ppm (about 0.08 mg/kg/day). At 8 ppm (0.29 mg/kg/day) the parental (Fo) males demonstrated increased heart and liver weights and the F1 generation had an increased incidence of hepatic centrilobular basophilic chromogenesis. The 40 ppm F1 groups showed increases in pup mortality, hepatic centrilobular basophilic chromogenesis, and severe chronic nephritis (males only).

The effects of HCB on adult animals has been further demonstrated in many other studies, a few of which report NOAELs. Kuiper-Goodman et al. (1977) exposed rats via the diet to 0, 0.5, 2, 8 and 32 mg/kg bw/day for up to 15 weeks. A NOAEL was reported at 0.5 mg/kg/day, while at the higher dose levels, increased tissue porphyrin, increased organ weights and increased severity of centrilobular liver lesions were noted. Grant et al. (1974) exposed rats to HCB at dietary levels of 10, 20, 40, 80 and 160 ppm for 9-10 months. Porphyria was induced at levels as low as 20 ppm (about 1 mg/kg/day).

The data selected for HNC determination are from the Arnold et al. (1985) study. This study involved the exposure of adult male and female Sprague-Dawley rats and subsequent exposure of the offspring in utero, via lactation, and via the diet. Cross-fostering studies have demonstrated that the neonate is particularly sensitive to the toxic effects of HCB. The transfer of HCB to neonates via the milk of exposed adults has also been shown to be significant (Bailey et al. 1980; Bleavins et al. 1982). The Arnold et al. (1985) study demonstrated NOAELs of 0.32 and 1.6 ppm in feed (estimated to be 0.016 and 0.08 mg/kg/day). Therefore, the NOAEL of 0.08 mg/kg/day, with an uncertainty factor of 100 (10x for interspecies variation and 10x for intraspecies differences) is used for HNC derivation. Consideration was also given to the mink and ferret data (Rush et al., 1983; Bleavins et al., 1984a, 1984b) which demonstrate that these species are highly sensitive to the developmental toxic effects of HCB. Adverse effects on the development of mink and ferrets have been reported at doses only slightly higher than the rat NOAEL of 0.08 mg/kg/day. However, the rat NOAEL is utilized preferentially because the Sprague-Dawley rat, unlike the mink or ferret, has been extensively studied as an animal model for toxicity testing, and the high quality of the Arnold et al. (1985) study. The selection of this key study is consistent with EPA's RfD for HCB (1988).

$$ADE = \frac{NOAEL}{UF} = \frac{0.08\ mg/kg/d}{100} = 8 \times 10^{-4}\ mg/kg/day$$

Where: Uncertainty Factor = 100, composed of:

10x for interspecies variability
10x for intraspecies differences

Drinking Water Sources:

$$HNV = \frac{ADE \times BW \times RSC}{WC_d + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{8 \times 10^{-4} \text{ mg/kg/d} \times 70 \text{ kg} \times 0.8}{2 \text{ l/d} + [(0.0036 \times 43{,}690) + (0.0114 \times 71{,}080)]}$$

$$= 4.6 \times 10^{-2} \text{ ug/L}$$

Non-Drinking Water Sources:

$$HNV = \frac{ADE \times BW \times RSC}{WC_r + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{8 \times 10^{-4} \text{ mg/kg/d} \times 70 \text{ kg} \times 0.8}{0.01 \text{ l/d} + [(0.0036 \times 43{,}690) + (0.0114 \times 71{,}080)]}$$

$$= 4.6 \times 10^{-2} \text{ ug/L}$$

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U.S. Environmental Protection Agency (EPA). 1985a. Drinking Water Criteria Document for Hexachlorobenzene (Final Draft). EPA - 600/X-84-179-1. PB-86-117777.

U.S. Environmental Protection Agency (EPA). 1985b. Health Assessment Document for Chlorinated Benzenes. EPA/600/8-84/015F.

U.S. Environmental Protection Agency (EPA). 1988. Integrated Risk Information System (IRIS database). Chemical file for hexachlorobenzene (118-74-1). Verification Date 5/26/88. Last Revised 4/1/91.

Tier 1 Human Cancer Criterion

A review of the available literature indicates that there are inadequate human data, but sufficient animal carcinogenicity data to support a B2 weight-of-evidence classification (EPA, 1989). The animal bioassays, which have been comprehensively reviewed and summarized by EPA (1980; 1985a; 1985b; 1989), indicate that HCB induces tumors of the liver predominantly, with neoplasm induction of the thyroid and kidney also reported. The data are judged sufficient for Tier 1 HCC derivation.

EPA (1991) derived an oral slope factor of 1.6 $(mg/kg/day)^{-1}$ from a chronic rat bioassay demonstrating hepatocellular carcinoma induction (Erturk et al., 1986). This slope factor is among the highest of those derived for HCB from 14 different datasets, which fell within a range of 8.3 E-2 to 1.7 E+0 (EPA, 1989). This dataset was also selected for slope factor

estimation because the study was well-conducted and the tumors were malignancies of the primary target organ (liver cancers). In the key study, Erturk et al. (1986; abstracts previously published as Lambrecht et al., 1983a; 1983b) exposed groups of 94 Sprague-Dawley rats/sex/dose to HCB via feed at 0, 75 or 150 ppm in the diet for up to two years. Treated animals of both sexes surviving past 12 months showed significant increases in liver and renal tumors. Females were far more susceptible to hepatocarcinogenicity while males were generally more sensitive to renal carcinogenicity. The slope factor of 1.6 per (mg/kg)/day is derived from the induction of hepatocellular carcinomas in female rats. This is consistent with EPA (1989).

$$RAD = \frac{\text{Risk Level}}{q1^*} = \frac{1 \times 10^{-5}}{1.6\ (mg/kg/d)^{-1}}$$

$$= 6.25 \times 10^{-6}\ mg/kg/d$$

Drinking Water Sources:

$$HCV = \frac{RAD \times BW}{WC_d + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{6.25 \times 10^{-6}\ mg/kg/d \times 70\ kg}{2\ l/d + [(0.0036 \times 43{,}690) + (0.0114 \times 71{,}080)]}$$

$$= 4.5 \times 10^{-4}\ ug/L$$

Non-Drinking Water Sources:

$$HCV = \frac{RAD \times BW}{WC_r + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{6.25 \times 10^{-6}\ mg/kg/d \times 70\ kg}{0.01\ l/d + [(0.0036 \times 43{,}690) + (0.0114 \times 71{,}080)]}$$

$$= 4.5 \times 10^{-4}\ ug/L$$

References:

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GREAT LAKES WATER QUALITY INITIATIVE
TIER 1 HUMAN HEALTH CRITERIA FOR
HEXACHLOROETHANE
CAS NO. 67-72-1

Tier 1 Human Noncancer Criteria

A review of the available literature indicates that the most appropriate basis for HNV derivation for hexachloroethane (HCE) is the NOAEL from a 16-week dietary study in rats (Gorzinski et al., 1985; Gorzinski et al., 1980, as cited in EPA, 1991). In this study male and female CDF Fischer 344 rats (10/sex/group) were administered a diet containing HCE at target levels of 0, 3, 30 and 100 mg/kg/day for 16 weeks. EPA (1991) reported that actual dose levels were analyzed to be approximately 0, 1.3, 20 and 82 mg/kg/day. From analysis of eating patterns and measurement of the time-related loss of HCE from the diets, a conservative estimate of exposure was determined by the investigators as 0, 1, 15 and 62 mg/kg/day (Gorzinski et al., 1985). The results indicate that male rats were slightly more sensitive than female rats to the nephrotoxic properties of HCE. Renal toxicity observed at 15 and 62 mg/kg/day in male rats included pale and mottled kidneys; significant increases in absolute and relative kidney weights; slight to moderate renal tubular atrophy and degeneration with or without peritubular fibrosis; a slight to moderate increase in renal tubular cytoplasmic clumping and droplet formation; and scattered or isolated renal tubules with slight hypertrophy and/or dilation of the proximal convoluted tubules. Liver weights were increased in male rats given 62 mg/kg/day. The liver exhibited a slight swelling of the hepatocytes in males given 15 or 62 mg/kg/day. Evidence of renal toxicity in female rats consisted of very slight renal tubular atrophy and degeneration observed histopathologically at the highest dose level. Female rats given 62 mg/kg/day also had an increase in relative liver weight ratios unaccompanied by microscopic alterations. Based on this study, a NOAEL of 1 mg/kg/day was derived for liver and kidney toxicity in male rats. While EPA (1991) indicates a NOAEL of 1.3 mg/kg/day based on the analyzed low dose, the estimated NOAEL of 1.0 mg/kg/day (Gorzinski et al., 1985; EPA, 1987) is used in the HNV derivation.

In a chronic (78-week) gavage study with rats and mice, the National Cancer Institute (NCI, 1978) administered HCE in a cyclic manner to 50 male and 50 female Osborne-Mendel rats and continuously to 50 male and 50 female B6C3F1 mice. The rats received HCE in corn oil at doses of 250 and 500 mg/kg/day, 5 days per week for a period of 22 consecutive weeks, followed by a 1-week, treatment-free interval. Thereafter, until the end of the 78 weeks, the rats were intubated for 4 consecutive weeks followed by 1 treatment-free week, in a cyclical pattern, for a total of 66 weeks of HCE treatment. The time-weighted-average

doses for the rats for the 78-week period were 212 and 423 mg/kg/day. The mice were intubated orally with HCE in corn oil at initial levels of 500 and 1000 mg/kg/day for 8 weeks with these doses increased to 600 and 1200 mg/kg/day, respectively, for the remaining 70 experimental weeks. A time-weighted-average dose of 590 and 1179 mg/kg/day for the low and high doses, respectively, was reported. The dosing regimes were followed by an observation period of 33 or 34 weeks for rats and 12 or 13 weeks for mice. Renal tubular nephropathy was observed during histopathological examination at the termination of the study in all groups of treated animals. In rats, significant pathology and mortality at both dose levels in the males precluded the development of a NOAEL or LOAEL for HCE. For the mice, due to the occurrence of hepatocellular carcinoma and non-neoplastic toxic nephropathy in both sexes at both dose levels, neither a NOAEL nor a LOAEL could be determined.

Because of the inconclusive nature of results from the NCI (1978) study, additional toxicological and carcinogenesis studies were conducted by administering HCE in corn oil by gavage to groups of male and female F344/N rats (50/sex/group) 5 days per week for 2 years (NTP, 1989). The male rats received doses of 0, 10 or 20 mg/kg/day while the females received doses of 0, 80 or 160 mg/kg/day. The foremost toxic effect was kidney toxicity, demonstrated by increased incidence of mineralization and hyperplasia of the pelvic transitional epithelium in dosed male rats, increased severity of renal tubule hyperplasia in high dosed male rats, and increased incidence and severity of renal tubule hyperplasia in female rats. The LOAEL was 10 mg/kg bw/day for male rats. In this study, it was hypothesized that the increased sensitivity of male rats to the renal toxicity of HCE was a result of the accumulation of α_{2u}-globulin in hyaline droplets synthesized by the liver and secreted into the blood (EPA, 1991). It is then apparently filtered through the glomeruli and partially reabsorbed through the proximal tubules. In the presence of HCE, as well as several nonpolar hydrocarbons such as decalin and gasoline, α_{2u}-globulin accumulates in hyaline droplets in the renal tubular cells. α_{2u}-Globulin is an excretory protein in male but not female rats. This may explain the male's greater sensitivity to kidney damage from HCE.

In a 13-week rat study, also by NTP (1989), groups of 10 F344/N rats of each sex were administered 0, 47, 94, 188, 375 or 750 mg/kg HCE in corn oil by gavage, 5 days/week for 13 weeks. Five/10 male rats and 2/10 female rats at 750 mg/kg/day died before the end of the study. The final mean body weight of male rats that received 750 mg/kg/day was 19% lower than that of vehicle controls. Compound-related clinical signs for both sexes included hyperactivity at doses of $\geq$ 94 mg/kg/day and convulsions at $\geq$ 375 mg/kg/day. The relative weights of liver, heart and kidney were increased for exposed males and females. Kidney lesions were seen in all dosed male groups, and the severity increased with dose. Papillary necrosis and tubular cell

necrosis and degeneration in the kidney and hemorrhagic necrosis in the urinary bladder were observed in the five male rats at 750 mg/kg/day which died before the end of the study. At all lower doses in males, hyaline droplets, tubular regeneration, and granular casts were present in the kidney. No chemical-related kidney lesions were observed in females. Foci of hepatocellular necrosis were observed in several male and female rats at ≥ 188 mg/kg/day.

Weeks et al. (1979) studied the effects of repeated exposure to HCE vapor in 25 male and 25 female rats, 4 male dogs, 10 male guinea pigs, 20 male or female quail and 22 pregnant rats per exposure group. The animals were exposed for 6 hours/day, 5 days/week for 6 weeks and doses were analyzed at 0, 15, 48 or 260 ppm of the HCE vapor (equivalent to 0, 145, 465 or 2515 mg/m^3; EPA, 1991). Toxic effects at the highest concentrations included tremors and other neurotoxic signs. No effects were observed at ≤ 465 mg/m^3.

Weeks et al. (1979) performed an oral study, in which HCE doses of 100, 320 and 1000 mg/kg/day were administered by gavage to rabbits for 12 days. The two highest doses resulted in liver degeneration and necrosis, toxic tubular nephrosis of the convoluted tubules of the corticomedullary region of the kidney, minimal tubular nephrocalcinosis, and decreased body weights. The NOAEL for this study was 100 mg/kg/day based on the effects of HCE on the kidneys of male rabbits.

The database is judged to be sufficient for Tier 1 HNC derivation. The key study (Gorzinski et al., 1985) provides a subchronic NOAEL which is supported and supplemented by chronic toxicity data (EPA 1989; EPA, 1991; NCI, 1978; NTP, 1989; Weeks et al., 1979). The HNC is based on the subchronic rat NOAEL of 1 mg/kg/day, with a total uncertainty factor of 1000. The LOAEL of 15 mg/kg/day resulted in male rat renal toxicity. It may be argued that the high sensitivity of this endpoint is peculiar to male rats, secondary to hyaline droplet formation and α_{2u}-globulin accumulation. However, liver affects also occurred at a LOEL of 15 mg/kg/day. The use of the NOAEL of 1 mg/kg/day for risk assessment is consistent with the oral RfD development by EPA (1987) and the Lifetime Health Advisory (EPA, 1991).

$$ADE = \frac{NOAEL}{UF} = \frac{1.00\ mg/kg/d}{1000} = 1.0 \times 10^{-3}\ mg/kg/day$$

Where: Uncertainty Factor = 1,000, composed of:
10x for interspecies variability
10x for intraspecies differences
10x for subchronic exposure duration

Drinking Water Sources:

$$HNV = \frac{ADE \times BW \times RSC}{WC_d + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{1.0 \times 10^{-3} \text{ mg/kg/d} \times 70 \text{ kg} \times 0.8}{2 \text{ l/d} + [(0.0036 \times 371) + (0.0114 \times 532)]}$$

$$= 6.0 \text{ ug/L}$$

Non-Drinking Water Sources:

$$HNV = \frac{ADE \times BW \times RSC}{WC_r + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{1.0 \times 10^{-3} \text{ mg/kg/d} \times 70 \text{ kg} \times 0.8}{0.1 \text{ l/d} + [(0.0036 \times 371) + (0.0114 \times 532)]}$$

$$= 7.6 \text{ ug/L}$$

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Tier 1 Human Cancer Criterion

A review of the available literature for HCE carcinogenicity reveals a lack of adequate epidemiological data and two chronic oral rodent bioassays (NCI, 1978; NTP, 1989). EPA (1986) has classified HCE as a class C carcinogen (possible human carcinogen), based on the observation of carcinomas in one mouse strain after oral exposure (NCI, 1978). The data are judged to be sufficient for Tier 1 HCC derivation.

In a NCI study (NCI, 1978), Osborne-Mendel rats and B6C3F1 mice were orally intubated with HCE in corn oil. Groups of 50 rats per sex per dose were administered HCE over a 78-week period with an exposure protocol involving intermittent treatment-free intervals. The time-weighted-average doses were 212 or 423 mg/kg/day. The rats were then observed for an additional 33-34 weeks. Groups of 50 mice per sex per dose were administered HCE 5 days per week for 78 weeks at time-weighted-average doses of 590 or 1179 mg/kg/day, and were then observed for an additional 12-13 weeks. Due to an unusually high mortality rate among the male control mice, the results in treated groups were compared against both the vehicle control group from this study as well as a pooled vehicle control group from several concurrent studies. A statistically significant increase in the incidence of hepatocellular carcinoma was reported in both sexes of the mice (only males exhibited a dose-related trend) while tumorigenicity was not observed in rats of either sex. The increased incidence was significant by the Cochran-Armitage test for both sexes of mice against both control groups and by the Fisher exact tests for both sexes as compared to the pooled controls. Survival of low- and high-dose male and female rats in this study was reduced compared with that of the vehicle controls.

Because findings from NCI (1978) in rats were inconclusive, additional studies on toxicity and carcinogenesis were conducted in F344/N rats by administering HCE in corn oil by gavage to groups of males and females for 2 years (NTP, 1989). HCE was administered 5 days/week in corn oil by gavage at 0, 10 or 20 mg/kg bw to groups of 50 male rats, and at 0, 80 or 160 mg HCE/kg bw to groups of 50 female rats. The incidence of renal adenomas and carcinomas alone and in combination increased in the high dose male group. One of the carcinomas in the high dose group metastasized to the lung. No compound-related neoplasms were observed in females. The incidence of pheochromocytomas of the adrenal gland in low dose male rats was significantly greater than that in vehicle controls, and the incidence for both dosed

groups were greater than the mean historical control incidence rates. The renal lesions were considered by NTP to be indicative of HCE carcinogenicity while the pheochromocytomas were judged to be supportive evidence for carcinogenic effects. On the basis of these data, NTP concluded that there was clear evidence of carcinogenicity for HCE in the male rat and no evidence of carcinogenicity in female rats. Renal tubule hyperplasia was observed at an increased incidence in high dose male rats. These lesions have been described as characteristic of the hyaline droplet nephropathy that is associated with an accumulation of liver-generated $\alpha_{2\mu}$-globulin in the cytoplasm of tubular epithelial cells (NTP, 1989). Using this assumption, it can be hypothesized that the male rat renal tumors were a secondary effect to hyaline droplet formation and that they may not be relevant to human risk assessment.

The Tier 1 Human Cancer Criteria for HCE are derived from the slope factor of 1.4 E-2 $(mg/kg/d)^{-1}$ based on a dose-response data-set for hepatocellular carcinoma induction in male mice from the NCI study (NCI, 1978; EPA, 1986).

$$RAD = \frac{\text{Risk Level}}{q1^*} = \frac{1 \times 10^{-5}}{1.4 \times 10^{-2}\ (mg/kg/d)^{-1}}$$

$$= 7.14 \times 10^{-4}\ mg/kg/d$$

Drinking Water Sources:

$$HCV = \frac{RAD \times BW}{WC_d + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{7.14 \times 10^{-4}\ mg/kg/d \times 70\ kg}{2\ l/d + [(0.0036 \times 371) + (0.0114 \times 532)]}$$

$$= 5.3\ ug/L$$

Non-Drinking Water Sources:

$$HCV = \frac{RAD \times BW}{WC_r + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{7.14 \times 10^{-4}\ mg/kg/d \times 70\ kg}{0.01\ l/d + [(0.0036 \times 371) + (0.0114 \times 532)]}$$

$$= 6.7\ ug/L$$

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GREAT LAKES WATER QUALITY INITIATIVE
TIER I HUMAN HEALTH CRITERIA FOR
LINDANE
(GAMMA-HEXACHLOROCYCLOHEXANE)
CAS NO. 58-89-9

Tier 1 Human Noncancer Criterion

A review of the available literature indicates that the most appropriate study for the derivation of the HNV for lindane is a subchronic study conducted by Zoecon Corporation (1983) as evaluated by EPA (1991) and summarized by EPA (1986). In this study, Wistar KFM-Ham (outbred) SPF rats (20/sex/dose) were administered 0, 0.2, 0.8, 4, 20 or 100 ppm lindane in the feed. Fifteen animals/sex/group were sacrificed after 12 weeks. The remaining rats were fed the control diet for an additional six weeks before sacrifice. Rats exposed to 20 and 100 ppm lindane had a greater incidence of liver hypertrophy, kidney tubular degeneration, hyaline droplets, tubular distension, interstitial nephritis and basophilic tubules than did the controls. The NOAEL for this study was 4 ppm. This dose was estimated to be equivalent to 0.29 mg/kg/d for the male and 0.33 mg/kg/d for the female rats.

Two chronic studies which examined the effects of lindane on rats and dogs were cited by EPA (1986). A two-year study by Fitzhugh (1950) reported a NOAEL of 2.5 mg/kg/d in Wistar rats with liver weights and liver damage evaluated as the endpoints. In a two-year study in beagle dogs, Rivett et al. (1978) reported a NOAEL of 1.6 mg/kg/d for liver toxicity.

A review of the database on developmental and reproductive effects of lindane suggests that these effects may occur at levels higher than the NOAEL calculated in the study conducted by Zoecon Corporation (1983). Palmer et al. (1978a) found no adverse effects on reproductive function and development following exposure of female rats to lindane in the feed at levels of 1.25, 2.5 and 5 mg/kg/d for three generations. Khera et al. (1979) found no reproductive effects in Wistar rats exposed to lindane at levels ranging from 6.25 to 25 mg/kg from the 6th to the 15th day of gestation. No adverse effects were found in a teratogenicity study on pregnant rabbits fed lindane on gestation days 6-18 at levels of 5, 10 and 15 mg/kg (Palmer et al., 1978b). However, Sircar and Lahiri (1989) reported that even the lowest exposure group (3.75 mg/kg/d) of Swiss mice receiving lindane during gestation experienced reproductive failure.

The quality of the study conducted by Zoecon Corporation (1983) was deemed sufficient to derive a Tier 1 HNC. The results of studies which examine the reproductive or developmental effects of lindane are either negative or indicative of possible effects at doses substantially higher than the NOAEL reported by Zoecon Corporation (1983). Although subchronic in duration (12 weeks), the key study is supported by chronic studies in the

database. This study was also used by EPA (1986) to derive the oral RfD for lindane. The HNC was derived from the female rat NOAEL (0.33 mg/kg/d) using an uncertainty factor of 1000 to account for interspecies variability, intraspecies differences and subchronic exposure duration. The magnitude of this uncertainty factor is expected to result in adequate protection from any potential reproductive or developmental effects as well as chronic noncancer effects.

$$ADE = \frac{NOAEL}{UF} = \frac{0.33\ mg/kg/d}{1000} = 3.3 \times 10^{-4}\ mg/kg/day$$

Where: Uncertainty Factor = 1,000, composed of:
10x for interspecies variability
10x for intraspecies differences
10x for subchronic exposure duration

Drinking Water Sources:

$$HNV = \frac{ADE \times BW \times RSC}{WC_d + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{3.3 \times 10^{-4}\ mg/kg/d \times 70\ kg \times 0.8}{2\ l/d + [(0.0036 \times 1{,}926) + (0.0114 \times 2{,}636)]}$$

$$= 4.7 \times 10^{-1}\ ug/L$$

Non-Drinking Water Sources:

$$HNV = \frac{ADE \times BW \times RSC}{WC_r + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{3.3 \times 10^{-4}\ mg/kg/d \times 70\ kg \times 0.8}{0.01\ l/d + [(0.0036 \times 1{,}926) + (0.0114 \times 2{,}636)]}$$

$$= 5.0 \times 10^{-1}\ ug/L$$

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Tier I Human Cancer Criterion

EPA is currently reviewing the carcinogenicity for lindane. When this review is completed, EPA will evaluate whether there is sufficient data to derive a Tier I human cancer criterion for lindane.

GREAT LAKES WATER QUALITY INITIATIVE
TIER 1 HUMAN HEALTH CRITERIA FOR
MERCURY
CAS NO. 7439-97-6
(INCLUDING METHYLMERCURY, CAS NO. 22967-92-6)

Tier 1 Human Noncancer Criterion

A review of the available literature on the environmental cycling, fate, and toxicity of mercury and mercury compounds indicates that HNC derivation is most appropriately based upon the human dose-response to methylmercury. Numerous reviews on mercury toxicity (e.g., WHO, 1976; 1990; EPA, 1980; 1984a; 1984b; 1985a) describe the human dose-response relationship resulting from food-borne exposure to methylmercury in Iraq (1971-72), Japan (1940s thru 1960s), and elsewhere. These data are judged to be sufficient for Tier 1 criterion derivation.

Studies of widespread human food-borne exposure to methylmercury in fish (Minamata and Niigata, Japan) and in seed grain (Iraq) have shown that neurological symptoms of mercury toxicity in adults appear with blood levels of mercury in the range of 200 to 500 ng/ml (Nordberg and Strangert, 1976; Clarkson et al., 1976; WHO, 1976; 1990; EPA, 1980; 1984a; 1984b; 1985a). However, there are a few studies of workers exposed occupationally to mercury via inhalation which suggest that blood mercury levels as low as 10-20 ng/ml may result in the development of signs of renal dysfunction (increased proteinurea and albuminurea) and abnormal psychomotor performance (Roels et al., 1982; Piikivi et al., 1984; Buchet et al., 1980). The adult LOAEL of 200 ng/ml in blood has been associated with an intake level of 200-500 ug/d (EPA, 1980; WHO, 1990), although the human adult population's variability in mercury elimination rate is significantly bimodal (Clarkson et al, 1976; Nordberg and Strangert, 1976). The human LOAEL of 200 ug/d, or 3 ug/kg/d, for the development of neurological effects forms the basis for the RfD derived by EPA (1985b) and the fish consumption criteria derived by EPA (1980). It has been estimated that less than 5% of the adult population will experience neurological effects at these levels (WHO, 1990).

Risk assessments by EPA (1980) and EPA (1985b) utilized a total uncertainty factor of 10 in conjunction with the LOAEL dose, and both stated that the LOAEL and the risk assessment addressed the sensitivity and the adequate protection of both pre- and postnatal exposures. EPA (1980) justified the 10-fold uncertainty factor as an accounting for "individual differences in habits of fish consumption and in susceptibility to the toxic effects of methylmercury, including prenatal exposures". EPA (1985b) justified the 10-fold uncertainty factor "to adjust the LOAEL to what is expected to be a NOAEL. Since the effects are seen in sensitive individuals for chronic exposure, no additional factors are deemed necessary".

For the derivation of the Tier 1 Human Noncancer Criterion, a total uncertainty factor of 50 will be utilized. This is composed of a 10-fold factor to adjust the adult LOAEL to a presumed adult NOAEL and an additional 5-fold factor to protect CNS development during the sensitive fetal life stages. The use of a 10-fold factor for LOAEL-to-NOAEL conversion is justified by consideration of the severity and irreversibility of the effects at the LOAEL, the long latency of mercury effects, and the occupational studies which suggest that the threshold may be considerably lower than 200 ng Hg/ml blood.

An uncertainty factor of 5 is utilized to ensure that the criterion will be protective of the fetal effects of mercury exposure via maternal ingestion of mercury-contaminated fish. The particular sensitivity of the fetus has been recognized in reviews of mercury toxicity (WHO, 1976; 1990; D'Itri, 1978; EPA, 1980; 1984a; 1984b; 1985a). The earliest of these assessments (WHO, 1976) developed a dose-response relationship for the adult which was not presented as being accurate for the more sensitive fetal effects. It was noted that many infant victims reported from Minamata had severe cerebral involvement (palsy and retardation) whereas their mothers had mild or no manifestations of poisoning. Although these observations were qualitatively confirmed by animal studies, quantification of the difference in the degree of sensitivity between human fetuses and adults has been elusive. EPA (1980; 1985b) utilized a total uncertainty factor of 10 and assumed that the resulting risk assessments were adequately protective of fetal effects. However, WHO (1990) reviewed the database on oral methylmercury ingestion, including more recent studies, and made significant advances in delineating quantitatively the greater sensitivity of prenatal exposure relative to adult exposure. Although WHO (1990) did not recommend a particular numeric sensitivity factor for the fetus, their assessment sufficiently demonstrates that an additional uncertainty factor is reasonable and prudent to help ensure adequate protection. They concluded that adult effects occur at a LOAEL (for 5% increased occurrence rate) of 200 ng/ml blood, or at 50 ug/g in hair. Fetal effects on CNS development occur at a LOAEL (5% increased occurrence rate) of 10-20 ug/g as a peak level in maternal hair. Since the level of mercury in maternal blood correlates to the simultaneous level in new hair growth, the hair serves as a fairly reliable indicator of maternal blood mercury levels during pregnancy. The data suggest that the fetal effects LOAEL may be 2.5 to 5 times lower than the adult effects LOAEL.

The HNC is derived from the adult LOAEL dose of 3 ug/kg/d which is associated with the LOAEL in blood of 200 ng/ml, and an uncertainty factor of 50. The methylmercury form is the most significant of the mercury compounds from the standpoint of ambient environmental mercury and human exposures and health impacts. Aqueous concentrations of mercury, and especially methylmercury, may be very low in ambient waters. Other forms of mercury, such as elemental mercury or mercury (I), may be

reasonably anticipated to be transformed predominantly to methylmercury in the aquatic environment via oxidation to mercury (II) and biomethylation. The biomethylation of inorganic mercury and the very high propensity for methylmercury to bioaccumulate in aquatic organisms result in a high and significant human exposure potential (EPA, 1980; D'Itri, 1990; Annett et al., 1975). The various forms of mercury released to and found in the ambient aquatic environment may be assumed to be converted primarily to methylmercury. Therefore, the HNC is expressed as the total recoverable mercury concentration. Finally, a body weight of 65 kg was used instead of a body weight of 70 kg because of the potential fetal effects of mercury exposure via maternal ingestion of mercury-contaminated fish.

$$ADE = \frac{NOAEL}{UF} = \frac{3.0 \times 10^{-3}\ mg/kg/d}{50} = 6.0 \times 10^{-5}\ mg/kg/day$$

Where: Uncertainty Factor = 50, composed of:
10x for use of LOAEL instead of NOAEL
5x for intraspecies differences
(protection of fetal CNS development)

Drinking Water Sources:

$$HNV = \frac{ADE \times BW \times RSC}{WC_d + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{6.0 \times 10^{-5}\ mg/kg/d \times 65\ kg \times 0.8}{2\ l/d + [(0.0036 \times 27{,}900) + (0.0114 \times 140{,}000)]}$$

$$= 1.8 \times 10^{-3}\ ug/L$$

Non-Drinking Water Sources:

$$HNV = \frac{ADE \times BW \times RSC}{WC_r + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{6.0 \times 10^{-5}\ mg/kg/d \times 65\ kg \times 0.8}{0.01\ l/d + [(0.0036 \times 27{,}900) + (0.0114 \times 140{,}000)]}$$

$$= 1.8 \times 10^{-3}\ ug/L$$

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Tier 1 Human Cancer Criterion

Mercury is not considered carcinogenic.

GREAT LAKES WATER QUALITY INITIATIVE
TIER I HUMAN HEALTH CRITERIA FOR
METHYLENE CHLORIDE
CAS NO. 75-09-2

Tier 1 Human Noncancer Criterion

A review of the literature indicates that hepatic and renal toxicities are characteristic critical effects of methylene chloride subchronic and chronic exposure (EPA, 1989). From animal studies on the chronic toxicity of methylene chloride, the most appropriate basis for HNV derivation is the NOAEL from the chronic oral rat study by the National Coffee Association (NCA, 1982; Serota, et al., 1986a). In this study, F344 rats (85/sex/group) received nominal doses of 0, 5, 50, 125 or 250 mg/kg/day of methylene chloride via drinking water exposure for 2 years. An induction of liver toxicity in the females was observed. Treatment-related histological alterations such as increases in hepatocellular foci and fatty changes in the liver were observed in rats of both sexes at nominal doses of ≥ 50 mg/kg/day. No treatment-related effects were noted in the rats administered the nominal dose of 5 mg/kg/day. The actual NOAEL doses were 5.85 and 6.47 mg/kg/day for males and females, respectively.

In addition to the rat drinking water study, Hazleton Labs conducted a 24-month study with B6C3F1 mice for the National Coffee Association (NCA, 1983; Serota et al., 1986b). In this study, mice were exposed to nominal doses of 0, 60, 125, 185, and 250 mg/kg/day of methylene chloride in drinking water for up to 24 months. Dose-related histomorphologic changes, such as proliferative hepatic lesions and enhanced amount of Oil Red O positive material, were observed in groups exposed to the highest dose of methylene chloride. The study reported a NOAEL of 185 mg/kg/day. Compared to the 5.85-6.47 mg/kg/day NOAEL in rats (NCA, 1982; Serota et al., 1986a), this study demonstrates a wide difference in the interspecies sensitivities to methylene chloride-induced toxic effects.

In a 2-year inhalation toxicity and oncogenicity study by Dow Chemical Co. (Nitschke et al., 1988), groups of Sprague-Dawley rats (90 male and 180 female) were exposed to 0, 50, 200, or 500 ppm methylene chloride for 6 hours/day, 5 days/week for 2 years. During the course of the study, all rats were monitored after each exposure for signs of toxicity, changes in body weight and food intake. Samples of liver tissue were analyzed for DNA synthesis as indicated by ^{3}[H]-thymidine uptake. Rats selected for interim necropsies and all the others (at the end of the study) were subjected to extensive gross pathologic, histopathologic, and serum chemistry evaluation. Data on DNA synthesis in the liver, pathology, histopathology, mortality, and other parameters were evaluated for statistically significant

differences between the exposed and controls groups. Pathologic and histopathologic data of the exposed groups indicated that the liver and kidney are the primary targets of methylene chloride toxicity. An increased incidence of hepatocellular vacuolization was observed in male and female rats exposed to 500 ppm of methylene chloride. In addition, elevated numbers of multinucleated hepatocytes were observed in female rats exposed to 500 ppm methylene chloride. The effects of methylene chloride at lower doses (50 and 200 ppm) were comparable with historical controls. Responses to chemical insult leveled off by 12 months in that the responses of female rats exposed to 500 ppm for the first 12 months were comparable to those of female rats exposed to the same concentration for 24 months. Based on these results, the authors concluded that 200 ppm (706.7 mg/m^3) is the NOAEL for methylene chloride by the inhalation route. This exposure may be converted to a daily administered dose of approximately 159 mg/kg/day, adjusting for 6 hours/day exposure and assuming that Sprague-Dawley rats breathe approximately 0.9 m^3/kg bw/day (EPA, 1988).

Burek et al. (1984) reported a 2-year inhalation study of methylene chloride with Sprague-Dawley rats and Golden Syrian Hamsters. In this study, rats and hamsters were exposed to 0, 500, 1500, and 3500 ppm of methylene chloride for 6 hours/day, 5 days/week for 2 years. Liver and mammary glands were the principal target tissues of methylene chloride inhalation toxicity in rats. Groups exposed to 500 to 3500 ppm methylene chloride showed increased incidence of hepatocellular vacuolization consistent with fatty changes, and the number of multinucleated hepatocytes in the female rats was elevated. After 18 months of exposure to the regimen, several characteristic lesions of liver and mammary glands were transformed to benign neoplasms (Burek et al., 1984).

The database is judged to be sufficient for Tier 1 HNC derivation. The key study (NCA, 1982; Serota et al. 1986a) provides a chronic oral NOAEL which is supported and supplemented by other oral and inhalation chronic toxicity data. EPA used this key study in the derivation of the oral RfD for risk assessment purposes (EPA, 1985a), and to derive lifetime health advisories for methylene chloride (EPA, 1985b). For the RfD derivation, EPA (1985a) used the male and female rat doses, respectively of 52.58 and 58.32 mg/kg/day for LOAELs, and 5.85 and 6.47 mg/kg/day for NOAELs for hepatic effects (NCA, 1982; Serota et al., 1986a). The HNC is derived from the NOAEL from the key study, 5.85 mg/kg/day to male rats.

$$ADE = \frac{NOAEL}{UF} = \frac{5.85\ mg/kg/d}{100} = 5.85 \times 10^{-2}\ mg/kg/d$$

Where: Uncertainty Factor = 100, composed of:
10x for interspecies variability
10x for intraspecies differences

Drinking Water Sources:

$$HNV = \frac{ADE \times BW \times RSC}{WC_d + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{5.85 \times 10^{-2}\ mg/kg/d \times 70\ kg \times 0.8}{2\ l/d + [(0.0036 \times 1) + (0.0114 \times 2)]}$$

$$= 1.6 \times 10^{3}\ ug/L$$

Non-Drinking Water Sources:

$$HNV = \frac{ADE \times BW \times RSC}{WC_r + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{5.85 \times 10^{-2}\ mg/kg/d \times 70\ kg \times 0.8}{0.01\ l/d + [(0.0036 \times 1) + (0.0114 \times 2)]}$$

$$= 9.0 \times 10^{4}\ ug/L$$

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Tier 1 Human Cancer Criterion

Methylene chloride is a class B2 carcinogen (a probable human carcinogen) according to the EPA weight-of-evidence classification of carcinogenic chemicals (EPA, 1989a). The classification rationale is based on sufficient evidence from animal carcinogenicity. Two epidemiological studies on chemical factory workers exposed to methylene chloride (Ott et al., 1983; Friedlander et al., 1978; Hearne et al., 1987) are inconclusive on the human carcinogenicity of methylene chloride. Review of these epidemiological studies and updated evaluation of the cohorts still provide inadequate evidence of human carcinogenicity .(EPA, 1989b). Experimental carcinogenesis studies indicate that exposure to methylene chloride by the oral route resulted in a significant increase in the incidence of hepatocellular carcinoma and neoplastic nodules in female F344 rats (NCA, 1982; Serota et al., 1986a) and male B6C3F1 mice (NCA, 1983; Serota et al, 1986b). Inhalation studies with methylene chloride produced an increased incidence of mammary tumors in both sexes of Sprague-Dawley (Burek et al., 1980, 1984) and F344 rats (NTP, 1986). The data are judged to be sufficient for Tier 1 HCC derivation.

The carcinogenic effects of methylene chloride via the oral route were investigated in two separate 2-year studies sponsored by the National Coffee Association (NCA, 1982, 1983; Serota et al., 1986a, 1986b). In the 1982 study, groups of 85 F344 rats of either sex received nominal doses of 5, 50, 125, or 250 mg/kg/day of methylene chloride in drinking water. Female rats receiving

50 and 250 mg/kg/day had a significantly increased incidence of combined hepatocellular carcinoma and neoplastic nodules in comparison to matched controls. Male rats, however, did not show an increased incidence of liver tumors. A dose-dependent, statistically significant increase in the incidence of salivary gland sarcoma was observed in male rats. A dose-related increase in the average number of benign mammary tumors was observed in female rats. The increased incidence of mammary tumors was observed in male rats, albeit to a lesser degree.

The National Coffee Association in its subsequent study (NCA, 1983; Serota et al., 1986b) exposed B6C3F1 mice of either sex to 0, 60, 125, 185, or 250 mg/kg/day methylene chloride in drinking water. A statistically significant increase in the incidence of combined hepatocellular carcinoma and neoplastic nodules was observed in male mice exposed to 125 and 185 mg/kg/day. However, only a marginal increase in the incidence of tumorigenesis and reduced average survival time was observed in the 250 mg/kg/day group.

Quantitative cancer risk estimates of methylene chloride are based on NTP inhalation studies in rats and mice (NTP, 1986). In this study, groups of 50 male and female F344/N rats and B6C3F1 mice were exposed to 0, 1000, 2000, and 4000 ppm (rats), and 0, 2000, and 4000 ppm (mice) for 6 hrs/day, 5 days/week for 102 weeks. Female rats, and to a lesser degree male rats, demonstrated a statistically significant increase in the incidence of mammary gland neoplasms. In mice, methylene chloride elicited an enhanced combined incidence of hepatocellular adenomas and carcinomas in the male (22/50, 24/49, 33/49) and female (3/50, 16/48, and 40/48) mice. Similarly, both male and female mice displayed an increased incidence of alveolar/bronchiolar adenomas and carcinomas (NTP, 1986).

In an inhalation study reported by Dow Chemical Company (Burek et al., 1980, 1984), Sprague-Dawley rats and Syrian Golden hamsters of both sexes were exposed to 0, 500, 1500, or 3500 ppm methylene chloride for 6 hrs/day, 5 days/week for 24 months. A statistically significant increased incidence of benign tumors in female hamsters exposed to 3500 ppm was attributed to increased longevity in that group. A statistically significant increase in salivary gland sarcoma was observed in male rats exposed to 3500 ppm methylene chloride. The finding of methylene chloride-induced salivary gland tumors in male rats is complicated by the observation that these rats had apparently contracted a viral disease, sialodacryoadentitis, in the salivary glands during the earlier phase of the exposure regimen (Burek et al., 1980, 1984). Based on these uncertainties, experimental results from this study were considered inconclusive on the carcinogenicity of methylene chloride. In a subsequent inhalation study by Dow Chemical Company (Nitschke et al., 1982), limited evidence of mammary fibroma/fibrosarcoma was observed in male and female rats exposed to 0, 50, 200, or 500 ppm of methylene chloride for 2 years.

EPA (1989b) derived a recommended oral slope factor from the arithmetic mean of two slope factors derived from the induction of liver tumors in female mice by inhalation (NTP, 1986) and in male mice by drinking water exposure (NCA, 1983; Serota et al., 1986b). These individual slope factors were 2.6×10^{-3} $(mg/kg/d)^{-1}$ and 1.2×10^{-2} $(mg/kg/d)^{-1}$, respectively (EPA, 1989b). This approach recommended by EPA (1989b) is utilized for Tier 1 HCC derivation, utilizing an arithmetic mean slope factor of 7.3×10^{-3} $(mg/kg/d)^{-1}$.

$$RAD = \frac{\text{Risk Level}}{q1^*} = \frac{1 \times 10^{-5}}{7.3 \times 10^{-3}\ (mg/kg/d)^{-1}}$$

$$= 1.37 \times 10^{-3}\ mg/kg/d$$

Drinking Water Sources:

$$HCV = \frac{RAD \times BW}{WC_d + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{1.37 \times 10^{-3}\ mg/kg/d \times 70\ kg}{2\ l/d + [(0.0036 \times 1) + (0.0114 \times 2)]}$$

$$= 47\ ug/L$$

Non-Drinking Water Sources:

$$HCV = \frac{RAD \times BW}{WC_r + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{1.37 \times 10^{-3}\ mg/kg/d \times 70\ kg}{0.01\ l/d + [(0.0036 \times 1) + (0.0114 \times 2)]}$$

$$= 2.6 \times 10^{3}\ ug/L$$

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Serota, D.G., A.K. Thakur, B.M. Ulland, J.C. Kirschman, N.M. Brown, R.H. Coots and K. Morgareidge. 1986a. A two-year drinking water study of dichloromethane on rodents. I. Rats. Food Chem. Toxicol. 24:951-958.

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GREAT LAKES WATER QUALITY INITIATIVE
TIER I HUMAN HEALTH CRITERIA FOR
POLYCHLORINATED BIPHENYLS (PCBS)
CAS NO. 1336-36-3

Tier 1 Human Noncancer Criterion

The database is judged insufficient for Tier 1 Human Noncancer Criterion development.

Tier 1 Human Cancer Criterion

PCBs (as a class) have sufficient carcinogenicity weight-of-evidence for a B2 classification (probable human carcinogen) based on the induction of hepatocellular carcinomas in three strains of rats and two strains of mice and inadequate yet suggestive evidence of excess risk of liver cancer in humans (EPA, 1987). The data are judged sufficient for Tier 1 HCC derivation. Although animal feeding studies demonstrate the carcinogenicity of commercial PCB preparations, it is not known which of the PCB congeners in such mixtures are responsible for these effects. EPA (1987) developed a carcinogenicity risk assessment for PCBs with a slope factor derived from Aroclor 1260 data, clearly stating the intent that the assessment be considered representative for all PCB mixtures. The application of this approach to regulatory programs is a prudent approach to ensure adequate protection of public health.

A review of the available carcinogenicity data indicates that the most appropriate studies for quantitative cancer risk assessment are the bioassays of Kimbrough et al (1975) and Norback and Weltman (1985). These studies utilized different rat strains -- Sherman rats in the Kimbrough et al (1975) study, Sprague-Dawley rats in the Norback and Weltman (1985) study -- but otherwise had several similarities. Both utilized large numbers of animals in chronic Aroclor 1260 feeding studies with only one exposure group. Dosed groups received 100 ppm for 630 days in the bioassay by Kimbrough et al. (1975), while Norback and Weltman (1985) administered 100 ppm for 16 months followed by a 50 ppm diet for an additional 8 months, then a basal diet for 5 months. The predominant neoplastic effect in each study was the increased incidence of hepatocellular neoplasms in female rats.

Using the linearized multistage procedure, EPA (1987) estimated slope factors of 7.7 $(mg/kg/d)^{-1}$ and 3.9 $(mg/kg/d)^{-1}$ from the data of Norback and Weltman (1985) and Kimbrough et al. (1975), respectively. The larger of these slope factors, 7.7 $(mg/kg/d)^{-1}$, was selected by EPA (1987) as the preferred slope factor estimate.

Although the Norback and Weltman (1985) study included a test protocol of partially hepatectomizing some of the animals, EPA (1987) noted that the study had favorable qualities. The rat strain used (Sprague-Dawley) is known to have a low incidence of

spontaneous hepatocellular neoplasms, the study duration spanned the natural life of the animal, and concurrent morphologic liver studies showed the sequential progression of liver lesions to hepatocellular carcinomas. Extrapolation modeling utilized a female rat liver tumor incidence rate of 45/47 in the dosed group. This includes 7 animals which had earlier undergone partial hepatectomy, and the liver tumor incidence for this subgroup was unreported. Exclusion of this group would have very little impact on the resulting slope factor, and the tumor promoting effect of the partial hepatectomization should be minimal (Hiremath, 1991). The Tier 1 Human Cancer Criterion for PCBs is based on the slope factor of 7.7 $(mg/kg/d)^{-1}$ derived from the rat bioassay of Norback and Weltman (1985).

$$RAD = \frac{\text{Risk Level}}{q1^*} = \frac{1 \times 10^{-5}}{7.7\ (mg/kg/d)^{-1}} = 1.30 \times 10^{-6}\ mg/kg/d$$

Drinking Water Sources:

$$HCV = \frac{RAD \times BW}{WC_d + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{1.30 \times 10^{-6}\ mg/kg/d \times 70\ kg}{2\ l/d + [(0.0036 \times 520{,}900) + (0.0114 \times 1{,}871{,}000)]}$$

$$= 3.9 \times 10^{-6}\ ug/L$$

Non-Drinking Water Sources:

$$HCV = \frac{RAD \times BW}{WC_r + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{1.30 \times 10^{-6}\ mg/kg/d \times 70\ kg}{0.01\ l/d + [(0.0036 \times 520{,}900) + (0.0114 \times 1{,}871{,}000)]}$$

$$= 3.9 \times 10^{-6}\ ug/L$$

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GREAT LAKES WATER QUALITY INITIATIVE
TIER 1 HUMAN HEALTH CRITERIA FOR
2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (2,3,7,8-TCDD).
CAS NO. 1746-01-6

Tier 1 Human Noncancer Criterion

Of the many subacute and chronic studies available for 2,3,7,8-TCDD, a few stand out as supporting Tier 1 criterion derivation. In a two-year toxicity and oncogenicity study, rats were administered doses of 0, 0.001, 0.01 and 0.1 ug/kg bw/day of 2,3,7,8-TCDD via diet (Kociba et al., 1978). Animals given the high dose exhibited increased mortality, decreased weight gain, slight depression of erythroid parameters, increased urinary excretion of porphyrins and delta-aminolevulinic acid and increased serum levels of certain enzymes. Histopathologic or gross effects were seen in liver, lymphoid, lung and vascular tissues. An increased tumor incidence was also seen. Similar effects, but to a lesser degree, were seen in mid-dose animals. A NOAEL of 0.001 ug/kg/day (1 ng/kg/day) was reported in this study.

A NOAEL of 0.001 ug/kg bw/day via feed exposure was also reported in a three-generation rat reproduction study (Murray et al., 1979). At 0.1 ug/kg/day, decreases in F_0 generation fertility and F_1 generation litter size were reported. At 0.01 ug/kg/day, significant decreases in fertility were seen in the F_1 and F_2 generations; other effects included decreased litter size at birth, decreased gestational survival and decreased neonatal growth and survival. The reproductive capacity of the low dose rats did not appear to be significantly affected in any generation. However, a reevaluation of these data using different statistical methods indicated that both lower dose levels resulted in significant reductions in offspring survival indices, increases in liver and kidney weight of pups, decreased thymus weight of pups, decreased neonatal weights and increased incidence of dilated renal pelvis (Nisbet and Paxton, 1982). Nisbet and Paxton (1982) concluded that 0.001 ug/kg/day (1 ng/kg/day) was not a NOEL in the Murray et al. (1979) study. Kimmel (1988) considered the data of Murray et al. (1979) to be suggestive of a pattern of decreased offspring survival and increased offspring renal pathology even at 0.001 ug/kg/day, although the pooling of data from different generations by Nisbet and Paxton (1982) was considered biologically inappropriate.

Studies by Schantz et al. (1979) and Allen et al. (1979) suggest that rhesus monkeys are more sensitive to 2,3,7,8-TCDD than rats. When monkeys were administered 50 ppt 2,3,7,8-TCDD in feed for 7 to 20 months, decreases in fertility, increases in abortions and other toxic effects (alopecia, hyperkeratosis, weight loss, decreased hematocrit and white blood cell count and increased serum levels of SGPT) were noted. The 50 ppt dietary

residue level corresponds to a daily dose of 1.5 ng/kg bw/day (EPA, 1984). Therefore, 1.5 ng/kg/day can be considered a LOAEL for rhesus monkeys from these studies.

In a continuation of the rhesus monkey studies by Schantz et al. (1979) and Allen et al. (1979), Bowman et al. (1989a, 1989b) have evaluated the effects of 5 and 25 ppt 2,3,7,8-TCDD in feed on reproduction and on behavior, respectively. Breeding of the animals after 7 and 24 months of exposure resulted in impaired reproductive success at 25 ppt but not at 5 ppt (approximately 0.67 and 0.13 ng/kg bw/day, respectively). The exposures were discontinued after 4 years, and a third breeding ten months post-exposure did not indicate reproductive impairment (Bowman et al., 1989a). The offspring from these breeding experiments were evaluated for development and behavioral effects utilizing several testing methods (Bowman et al., 1989b). Although there were no significant effects of TCDD exposure on birth weight, growth, or physical appearance of the offspring, some behavioral test results were interpreted to be indicative of TCDD effects. These included alterations in the social behavior between the mothers and their infants and of peer groups of the offspring after weaning. However, the study groups were very limited in size and the statistical and biological significance of the findings are unclear. This study may be interpreted to provide only suggestive evidence of possible behavioral effects. The reproduction study of Bowman et al. (1989a) provides much clearer evidence of a LOAEL at 25 ppt (0.67 ng/kg/day) and a NOAEL at 5 ppt (0.13 ng/kg/day).

The EPA has used the equivocal evidence for a rat LOAEL at 1 ng/kg/day, supported by an unequivocal rhesus monkey LOAEL at 1.5 ng/kg/day, in the development of an Acceptable Daily Intake (ADI) (EPA. 1984; 1985a) and Drinking Water Equivalent Level (DWEL) (EPA, 1985b; 1990). In light of the more recent rhesus monkey study of Bowman et al. (1989a), there is improved resolution of the threshold for the sensitive effect of reproductive impairment in this species. The Human Noncancer Criterion is based on the NOAEL of 0.13 ng/kg/day (1.3×10^{-7} mg/kg/d) for reproductive effects from this study. The entirety of the rhesus monkey studies, supported by the evidence in rats cited above, is judged sufficient for Tier 1 criterion development.

$$\text{ADE} = \frac{1.3 \times 10^{-7} \text{ mg/kg/d}}{100} = 1.3 \times 10^{-9} \text{ mg/kg/d}$$

Where: Uncertainty Factor = 100, composed of:
10x for interspecies variability
10x for intraspecies differences

Drinking Water Sources:

$$HNV = \frac{ADE \times BW \times RSC}{WC_d + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{1.30 \times 10^{-9} \text{ mg/kg/d} \times 70 \text{ kg} \times 0.8}{2 \text{ l/d} + [(0.0036 \times 48{,}490) + (0.0114 \times 79{,}420)]}$$

$$= 6.7 \times 10^{-8} \text{ ug/L}$$

Non-Drinking Water Sources:

$$HNV = \frac{ADE \times BW \times RSC}{WC_r + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{1.30 \times 10^{-9} \text{ mg/kg/d} \times 70 \text{ kg} \times 0.8}{0.01 \text{ l/d} + [(0.0036 \times 48{,}490) + (0.0114 \times 79{,}420)]}$$

$$= 6.7 \times 10^{-8} \text{ ug/L}$$

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Tier 1 Human Cancer Criterion

The EPA (1984) evaluated the available epidemiological and animal bioassay data on the potential carcinogenicity of 2,3,7,8-TCDD. They determined that some case-control studies provide limited evidence for the human carcinogenicity of phenoxy acids and/or chlorophenols, which contain impurities including 2,3,7,8-TCDD. They concluded that the evidence for the human carcinogenicity of 2,3,7,8-TCDD based on the epidemiologic studies is only suggestive due to the difficulty of evaluating the risk of 2,3,7,8-TCDD exposure in the presence of the confounding effects of phenoxy acids and/or chlorophenol. Recently published epidemiology studies may be interpreted to provide suggestive evidence of carcinogenicity (Zober et al., 1990; Fingerhut et al., 1991). The potential use of these new studies for quantitative risk assessment has not yet been fully explored. With regard to animal bioassays, the EPA (1984) concluded that several rodent studies establish that 2,3,7,8-TCDD is an animal carcinogen in multiple species and organs and is probably carcinogenic in humans. The weight of evidence of carcinogenicity is sufficient for Group B2 classification (probable human carcinogen), and satisfies the database requirements for Tier 1 criterion derivation.

Among the carcinogenicity bioassays, NTP conducted bioassays with both Osborne-Mendel rats and B6C3F1 mice (NTP, 1982a). Groups of 50 mice and 50 rats of each sex were given 2,3,7,8-TCDD in corn oil-acetone by gavage twice per week for 104 weeks. Doses of 0, 0.01, 0.05 or 0.5 ug/kg/week were administered to

rats and male mice while female mice received 0, 0.04, 0.2 or 2.0 ug/kg/week. Controls consisted of 75 rats and 75 mice of each sex. Animals were killed at weeks 105-107. 2,3,7,8-TCDD caused an increased, dose-related incidence of follicular-cell adenomas or carcinomas of the thyroid in male rats. A significant increase in subcutaneous tissue fibromas was also seen in high-dose males. High-dose female rats exhibited increased incidence of hepatocellular carcinomas and neoplastic nodules, subcutaneous tissue fibrosarcomas and adrenal cortical adenomas. In male and female mice, 2,3,7,8-TCDD induced an increased dose-related incidence of hepatocellular carcinomas. High-dose female mice also exhibited increased incidence of thyroid follicular-cell adenomas.

In a dermal study also conducted under contract for NTP (NTP, 1982b), 30 male and 30 female Swiss Webster mice were treated with 2,3,7,8-TCDD in acetone for 3 days/week for 104 weeks. Doses of 0.005 ug and 0.001 ug 2,3,7,8-TCDD were administered to the clipped backs of males and females, respectively. A similar group was pretreated with one application of 50 ug dimethylbenzanthracene (DMBA) one week before 2,3,7,8-TCDD administration. 2,3,7,8-TCDD induced a statistically significant increase of fibrosarcomas in the integumentary system of females given both 2,3,7,8-TCDD alone and following a single application of DMBA.

Van Miller et al. (1977) administered diets containing 0, 0.001, 0.005, 0.05, 1, 50, 500 and 1000 ppb 2,3,7,8-TCDD to groups of 10 male Sprague-Dawley rats. Animals received the diets for 78 weeks and were then placed on control feed until they were killed at week 95. All rats fed the higher concentrations (1-1,000 ppb) died early. A variety of tumors were produced and the total number of animals with tumors generally increased, but the small number of animals limits the value of the data.

Kociba et al. (1978) administered 2,3,7,8-TCDD via the diet to groups of 50 male and 50 female Sprague-Dawley rats for 2 years. Control groups consisted of 86 animals of each sex. The doses administered were 0, 0.001, 0.01 and 0.1 ug/kg/day. 2,3,7,8-TCDD induced an increased incidence of hepatocellular carcinomas and hepatocellular hyperplastic (neoplastic) nodules in female rats at the two highest dose levels. The highest dose of 2,3,7,8-TCDD also induced an increase in the incidence of stratified squamous cell carcinomas of the hard palate and/or nasal turbinates in both males and females, squamous cell carcinomas of the tongue in males and squamous cell carcinomas of the lungs in females.

Kociba et al. (1978) is chosen as the basis for quantitative cancer risk assessment. The Kociba study found that the principal target organ for 2,3,7,8-TCDD-induced tumors was the liver in female rats, demonstrating a dose-related statistically significant increase of hepatocellular carcinomas and hyperplastic (neoplastic) nodules. For quantitative risk assessment, the data were adjusted for early mortality by

eliminating those animals that died during the first year of the study. Also, in the mid-dose group, two of the reported 20 females with tumors had both nodules and carcinomas; 18 affected animals were used as the input for the dose group. Using the linearized multistage model, the resulting slope factor for 2,3,7,8-TCDD is 1.51×10^{5} $(mg/kg/day)^{-1}$. However, an independent pathologist (Squire) was engaged by EPA to reevaluate the histopathologic slides from the Kociba study (EPA, 1984). Squire reported higher tumor incidence than Kociba, generating a slightly higher slope factor of 1.61×10^{5} $(mg/kg/day)^{-1}$. EPA (1984) used an average of the two slope factors, 1.56×10^{5} $(mg/kg/day)^{-1}$, to generate surface water criteria.

In March 1990 a panel of seven independent pathologists referred to as the Pathology Working Group (PWG) blindly reevaluated the female rat liver slides from Kociba et al. (1978). Liver lesions were classified according to the National Toxicology Program's 1986 liver tumor classification scheme (Sauer, 1990; Goodman and Sauer, 1992). Using the linearized multistage model, the liver tumor incidence rates reported by the PWG result in a slope factor of 5.1×10^{4} $(mg/kg/day)^{-1}$ for liver tumors only, and a slope factor of 7.5×10^{4} $(mg/kg/day)^{-1}$ for pooled significantly increased tumors of the liver, lung or nasal turbinates/hard palate. The latter method avoids double-counting of tumor-bearing animals (Bayard, 1990).

The Human Cancer Criterion is based on the pooled significant tumors in female rats of Kociba et al. (1978) with the liver tumor reevaluation of the Pathology Working Group (Sauer, 1990). The linearized multistage model generates a slope factor of 7.5×10^{4} $(mg/kg/day)^{-1}$ from these data.

$$RAD = \frac{\text{Risk Level}}{q1^*} = \frac{1 \times 10^{-5}}{7.5 \times 10^{4}\ (mg/kg/d)^{-1}}$$

$$= 1.33 \times 10^{-10}\ mg/kg/d$$

Drinking Water Sources:

$$HNV = \frac{RAD \times BW}{WC_d + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{1.33 \times 10^{-10}\ mg/kg/d \times 70\ kg}{2\ l/d + [(0.0036 \times 48{,}490) + (0.0114 \times 79{,}420)]}$$

$$= 8.6 \times 10^{-9}\ ug/L$$

Non-Drinking Water Sources:

$$HNV = \frac{RAD \times BW}{WC_r + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{1.33 \times 10^{-10} \text{ mg/kg/d} \times 70 \text{ kg}}{0.01 \text{ l/d} + [(0.0036 \times 48{,}490) + (0.0114 \times 79{,}420)]}$$

$$= 8.6 \times 10^{-9} \text{ ug/L}$$

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GREAT LAKES WATER QUALITY INITIATIVE
TIER 1 HUMAN HEALTH CRITERIA FOR
TOLUENE
CAS NO. 108-88-3

Tier 1 Human Noncancer Criterion

A review of the available literature indicates inadequate human data for quantitative risk assessment of toluene based on human health effects. Occupational exposure, cigarette smoking and deliberate inhalation of solvents found in various preparations ("glue sniffing") are common means of human exposure to toluene (NTP, 1990). Chronic exposure to toluene vapors at levels of approximately 200-800 ppm have been associated primarily with CNS effects, possibly peripheral nervous system effects, hepatomegaly and hepatic function changes, and renal function effects (EPA, 1987). Although these findings provide qualitative evidence of the human toxicity of toluene, specific exposure levels were not provided and these data do not provide a dose-response relationship (EPA, 1987; EPA, 1990; NTP, 1990).

The majority of the subchronic-chronic studies on toluene are inhalation studies determining behavioral or histopathologic effects of toluene exposure. The most appropriate basis for HNV derivation for toluene is the NOAEL from a 13-week rat gavage study (NTP, 1990). In this study, toluene in corn oil was administered by gavage to groups of weanling F344/N rats and B6C3F1 mice (10/sex/group) at dose levels of 0, 312, 625, 1250, 2500 or 5000 mg/kg, 5 days per week for 13 weeks. All rats at 5000 mg/kg died during the first week, and 8/10 rats at 2500 mg/kg died, two of which were due to gavage errors. Histopathologic changes were observed in the liver, kidney, brain and urinary bladder at ≥ 1250 mg/kg. The NOAEL for the rats is 312 mg/kg/day with a LOAEL based on liver and kidney weight changes in male rats at 625 mg/kg. Because the exposure was for 5 days/week, these doses are converted to time-weighted-average doses of 223 and 446 mg/kg/day, respectively (EPA, 1990).

As described above, NTP (1990) also conducted a 13-week gavage study in B6C3F1 mice. All mice that received 5000 mg/kg died during the first week, and 40% of those that received 2500 mg/kg died before the end of the 13-week gavage study. Clinical signs observed in mice at ≥ 2500 mg/kg included sub-convulsive jerking, prostration, impaired grasping reflex, bradypnea, hypothermia, hypoactivity and ataxia. The final mean body weight of males at 2500 mg/kg was lower than that of vehicle controls. At ≥ 1250 mg/kg, relative liver weights were increased for mice, but this increase was not statistically significant. The NOAEL for this study was 1250 mg/kg and the LOAEL was 2500 mg/kg. Adjusting the doses for 5 days/week exposure provides time-weighted-average NOAEL and LOAEL doses of 893 and 1786 mg/kg/day, respectively.

Another subchronic oral toxicity study was conducted by Wolf et al. (1956), in which female Wistar rats were administered

toluene by stomach tube at doses of 0, 118, 354 and 590 mg/kg/day, 5 days/week for a total of 138 doses (converted to time-weighted-average doses of approximately 0, 18, 253, and 422 mg/kg/day per EPA, 1990). No adverse effects were observed at any dose level in any of the parameters monitored: growth, appearance and behavior, mortality, organ/body weight, blood urea nitrogen levels, bone marrow counts, peripheral blood counts or morphology of major organs. The NOAEL for this study was 422 mg/kg/day as the time-weighted-average dose.

NYLAR mice were exposed pre- and post-natally to toluene provided in the drinking water at concentrations of 0, 16, 80 and 400 ppm (Kostas and Hotchin, 1981). Rotorod performance was measured at 45 and 55 days of age. An inverse dose-response relationship in the effects was noted in which rotorod performance was improved with increasing dose. No effects were observed for the following reproductive measurements: maternal fluid consumption, offspring mortality rate, development of eye or ear openings, or surface-righting response, resulting in a NOAEL of 400 ppm. Assuming mice consume water at appoximately 0.24 l/kg bw/day (EPA, 1988), the NOAEL was approximately 96 mg/kg/day.

Nawrot and Staples (1979) administered 0.3, 0.5 or 1.0 ml/kg bw toluene, 3 times/day (equivalent to approximately 780, 1300 and 2600 mg/kg/day, per EPA, 1990) to pregnant CD-1 mice from days 6-15 of gestation. No method of exposure was mentioned in this limited information abstract. Teratogenic effects were reported at 2600 mg/kg/day and increased embryolethality was reported at $\geq$ 780 mg/kg/day, therefore the LOAEL for this study was 780 mg/kg/day.

No other subchronic-chronic oral toxicity studies were identified in the available literature for toluene. Chronic inhalation studies include NTP (1990), in which F344/N rats and B6C3F1 mice (60/sex/dose) were exposed to vapors of toluene, 6.5 hours/day, 5 days/week for 2 years. Dose levels were 0, 120 (mice only), 600 or 1200 ppm. Ten animals/group (except male mice) were removed at 15 months for toxicologic evaluation. At 15 months, there was an increased incidence and severity in the erosion of olfactory epithelium, and degeneration of respiratory epithelium was increased in the exposed rats. At the end of the study inflammation of nasal mucosa and metaplasia of olfactory epithelium were increased in exposed females rats. Nephropathy was seen in almost all rats with a severity somewhat increased in exposed rats. For mice, no biologically relevant increase in any nonneoplastic lesion was observed.

Chronic inhalation of toluene was studied in F344 rats exposed to 30, 100 or 300 ppm (113, 377 or 1130 mg/m^3) toluene 6 hours/day, 5 days/week for 24 months (Gibson and Hardisty, 1983; CIIT, 1980, as cited in NTP, 1990; EPA, 1990; and EPA, 1987). A dose-related reduction in hematocrit values was reported in female rats exposed to 100 and 300 ppm. Increased corpuscular hemoglobin concentration was reported in females at 300 ppm.

In a perinatal study with CD-1 mice (Courtney et al., 1986), toluene was administered by inhalation at 200 and 400 ppm (750 and 1500 mg/m^3, respectively) to pregnant female CD-1 mice 7 hours/day from days 6-16 of gestation. Fetotoxicity was observed at 400 ppm with a significant shift in the fetal rib profile. An increased body weight in the neonates on day 1 postpartum was observed at 400 ppm. At 200 ppm, there was an increase in dilated renal pelves which the authors concluded might reflect desynchronization of maturation with respect to development and growth. Assuming that mice breathe appoximately 1.7 m^3/kg/day (EPA, 1988), the 7 hours/day 200 ppm LOAEL and 400 ppm FEL convert to approximately 370 and 740 mg/kg/day, respectively, as daily administered doses.

The Tier 1 HNC is derived from the NOAEL dose of 312 mg/kg (converted to 223 mg/kg/day for 5 days/week administration) from the 13-week oral rat study by NTP (1990) with an uncertainty factor of 1000. The uncertainty factor accounts for interspecies variation, intraspecies differences, and subchronic exposure duration. This approach should be protective of developmental effects, as suggested by the limited developmental toxicity data. This approach is consistent with the risk assessment of toluene for the oral RfD and the drinking water health advisory developed by EPA (1990; 1987).

$$ADE = \frac{223\ mg/kg/d}{1{,}000} = 2.23 \times 10^{-1}\ mg/kg/day$$

Where: Uncertainty Factor = 1,000, composed of:
10x for interspecies variability
10x for intraspecies differences
10x for subchronic exposure duration

Drinking Water Sources:

$$HNV = \frac{ADE \times BW \times RSC}{WC_d + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{2.23 \times 10^{-1}\ mg/kg/d \times 70\ kg \times 0.8}{2\ l/d + [(0.0036 \times 11) + (0.0114 \times 17)]}$$

$$= 5.6 \times 10^3\ ug/L$$

Non-Drinking Water Sources:

$$HNV = \frac{ADE \times BW \times RSC}{WC_r + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{2.23 \times 10^{-1}\ mg/kg/d \times 70\ kg \times 0.8}{0.01\ l/d + [(0.0036 \times 11) + (0.0114 \times 17)]}$$

= 5.1×10^4 ug/L

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Tier 1 Human Cancer Criterion

Toulene is not considered carcinogenic.

GREAT LAKES WATER QUALITY INITIATIVE
TIER 1 HUMAN HEALTH CRITERIA FOR
TOXAPHENE
CAS NO. 8001-35-2

Tier 1 Human Noncancer Criterion

EPA is currently reviewing the RfD for toxaphene. Because there is no EPA verified RfD that can be used for derivation of a Tier I human noncancer, the final Guidance does include a noncancer criterion for toxaphene.

Tier 1 Human Cancer Criterion

According to EPA (1985; 1987), there are inadequate data available to ascertain whether toxaphene is a human carcinogen. However, two chronic studies have shown that toxaphene induces the formation of liver tumors in B6C3F1 mice. One of these studies also found that toxaphene induces the formation of thyroid tumors in Osborne-Mendel rats. Toxaphene was mutagenic for Salmonella typhimurium strains TA98 and TA100 (Hill, 1977 as cited by EPA, 1985) and was also found to induce the formation of sister chromatid exchanges in Chinese hamster lung (DON) cells (Steinel et al., 1990). However, toxaphene produced a negative response in a modified dominant lethal assay which used male ICR/Ha Swiss mice (Epstein et al., 1972). According to EPA (1985; 1987), the weight-of-evidence for toxaphene carcinogenicity is sufficient for B2 classification (probable human carcinogen). The data are sufficient to derive a Tier 1 HCC.

In a study conducted by NCI (1979), 50 Osborne-Mendel rats/sex/group and 50 B6C3F1 mice/sex/group were administered toxaphene in their diets for 80 weeks. Male rats received time-weighted average (TWA) doses of 112 and 556 ppm, while females received TWA doses of 540 and 1080 ppm. Both male and female mice received TWA doses of 99 and 198 ppm. Both rats and mice had 10 matched controls/sex with an additional 45 pooled controls/sex for rats and 40 additional pooled controls/sex for mice. Male and female rats exhibited a statistically significant dose-related increased incidence of thyroid tumors (adenomas and carcinomas), whereas treated mice exhibited a statistically significant dose-related increased incidence of liver tumors (NCI, 1979).

In a study conducted by Litton Bionetics (1978, as cited by EPA, 1987), toxaphene was administered to B6C3F1 mice (54 mice/sex/group) in the diet for 18 months at doses of 0, 7, 20 and 50 ppm. Animals were observed for a period of 6 months after treatment. An increased incidence of hepatocellular tumors (adenomas and carcinomas) was seen in both sexes and was statistically significant in males administered 50 ppm. This

study, rather than the NCI study, was used for cancer risk assessment because it utilized more dose levels and a lower range of doses while still eliciting a tumorigenic response in the liver. EPA (1987) recommends the same key study and slope factor ($1.1\ (mg/kg/d)^{-1}$) as utilized for HCC derivation.

$$RAD = \frac{\text{Risk Level}}{q1^*} = \frac{1 \times 10^{-5}}{1.1\ (mg/kg/d)^{-1}}$$

$$= 9.09 \times 10^{-6}\ mg/kg/d$$

Drinking Water Sources:

$$HNV = \frac{RAD \times BW}{WC_d + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{9.09 \times 10^{-6}\ mg/kg/d \times 70\ kg}{2\ l/d + [(0.0036 \times 498{,}100) + (0.0114 \times 665{,}600)]}$$

$$= 6.8 \times 10^{-5}\ ug/L$$

Non-Drinking Water Sources:

$$HNV = \frac{RAD \times BW}{WC_r + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{9.09 \times 10^{-6}\ mg/kg/d \times 70\ kg}{0.01\ l/d + [(0.0036 \times 498{,}100) + (0.0114 \times 665{,}600)]}$$

$$= 6.8 \times 10^{-5}\ ug/L$$

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GREAT LAKES WATER QUALITY INITIATIVE
TIER 1 HUMAN HEALTH CRITERIA FOR
TRICHLOROETHYLENE
CAS NO. 79-01-6

Tier 1 Human Noncancer Criterion

EPA is currently reviewing the RfD for trichloroethylene. Because there is no EPA verified RfD that can be used for derivation of a Tier I human noncancer, the final Guidance does include a noncancer criterion for trichloroethylene.

Tier 1 Human Cancer Criterion

Six epidemiologic studies have been performed to investigate the carcinogenicity of trichloroethylene (TCE) in exposed workers (Axelson et al., 1978; Hardell et al., 1981; Malek et al., 1979; Novotna et al., 1979; Paddle, 1983; Tola et al, 1980). Results of those studies were inadequate to attribute cancer incidence to TCE exposure. However, because they suffer from various limitations and deficiencies, they also fail to provide adequate evidence that TCE is not a human carcinogen (EPA, 1985).

Based on weight of evidence, EPA (1985, 1987, 1988) classified TCE in Group B2- Probable Human Carcinogen. The evidence reviewed by EPA (1985) for carcinogenicity of TCE in experimental animals includes increased incidence of hepatocellular carcinomas in male and female B6C3F1 mice (NCI, 1976; NTP, 1982, 1986) by gavage, malignant lymphomas in female Han:NMRI mice by inhalation (Henschler et al., 1980); and renal adenocarcinomas in male Fischer 344 rats by gavage (NTP, 1982, 1986). Evidence presented in EPA (1987) markedly strengthened the B2 classification by showing that inhalation is a second exposure route that results in carcinogenic activity in rats and mice, and by identifying diverse tumor sites (EPA, 1987).

EPA (1985) developed a quantitative cancer risk assessment based on four sets of gavage bioassay data that show hepatocellular carcinomas in male and female mice (NTP, 1982; NCI, 1976). The NCI bioassay involved exposure by gavage to B6C3F1 mice. Although rats were also tested, excessive mortality in all groups cast doubt on the adequacy of those results. Mice were dosed in groups of 50 animals per sex, 5 days/week for 78 weeks. Surviving animals were sacrificed at 90 weeks and subjected to complete necropsy and histopathological examination. The time-weighted-average (TWA) doses for male mice were 1,169 and 2,339 mg/kg, and for the female mice they were 869 and 1,739 mg/kg. The study included 20 matched vehicle control animals of each sex. It was concluded that TCE induced a statistically significant ($p < 0.05$) increase in the incidence of hepatocellular carcinoma in both male and female B6C3F1 mice. A reduction in the time-to-tumor response was also reported among male mice at the high dose level. The presence of the trace contaminant epichlorohydrin (0.09%) in the test material for this

bioassay could be a cause for concern. However, it has been determined that any potential contribution of epichlorohydrin to the overall carcinogenic potency of TCE in the bioassay was negligible (EPA, 1985).

NTP (1982) conducted a carcinogenicity bioassay on TCE in B6C3F1 mice and F344/N rats. The rats experienced reduced survival when compared to controls, and the results were therefore invalidated. Male and female mice were dosed by gavage at 1,000 mg/kg, 5 days/week for 103 weeks. Survival was significantly lower ($p < 0.004$) in treated males whereas survival in treated females was lower after 95 weeks, but the overall difference between vehicle controls and treated females was not significant. Male and female mice had a statistically significant increase in the incidence of hepatocellular carcinoma ($p \leq 0.002$) and hepatocellular adenoma ($p \leq 0.05$) over corresponding vehicle controls. The TCE test material for that bioassay was not contaminated with detectable amounts of epichlorohydrin. The potency of TCE with regard to the induction of hepatocellular carcinomas in mice has been determined to be very similar in the NTP (1982) bioassay and the NCI (1976) bioassay (EPA, 1985).

Additional studies were reviewed by EPA (1987) identifying positive findings by inhalation exposure in rats and mice. Maltoni et al. (1986) conducted bioassays of Sprague-Dawley rats exposed to 0, 100, 300 and 600 ppm of TCE 7 hours/day, 5 days/week for 104 weeks. Necropsy was performed on all animals. Male rats demonstrated increased incidence of renal tubuli megalonucleocytosis and renal adenocarcinomas, and a slight increase in leukemias, particularly immunoblastic lymphosarcomas. Maltoni et al. (1986) also conducted bioassays on Swiss mice and B6C3F1 mice (90 mice/strain/sex/group) exposed to 0, 100, 300, and 600 ppm TCE for 78 weeks. Statistically significant increases in hepatomas were noted among male Swiss mice at the high concentration, and significant increases in pulmonary tumors were observed among male Swiss mice at high and medium exposures. Among the B6C3F1 mice, there were increases in hepatomas in males and females, pulmonary tumors in females, and in the total number of tumors among females at all concentrations.

Fukuda et al., (1983) reported the results of bioassays with female ICR mice and Sprague-Dawley rats (49-50 per group) exposed to airborne concentrations of 0, 50, 150, and 450 ppm of TCE for 7 hours/day, 5 days/week for 107 weeks. There were no statistically significant increases in tumors among rats, however a statistically significant increase in lung adenocarcinomas was found among the mice.

Using the mice liver tumor data sets from NTP (1982) and NCI (1976), EPA (1985) calculated human slope estimates of 1.9×10^{-2}, 8.0×10^{-3}, 1.8×10^{-2}, and 5.8×10^{-3} $(mg/kg/day)^{-1}$. Because the slope estimates from these four data sets were found to be comparable, their geometric mean was used to derive the recommended slope factor of 1.1×10^{-2} $(mg/kg/day)^{-1}$. EPA (1987)

also developed slope factors from the inhalation studies of Maltoni et al. (1986) and Fukuda et al.(1983). These slope factors were found to be comparable to the q_1^* developed earlier from the gavage studies (EPA, 1987).

EPA is currently reviewing the carcinogenicity data for trichloroethylene. Based on this review EPA may change the carcinogenicity characterization for trichloroethylene. However, until this review is completed the previously verified oral slope factor of 1.1×10^{-2} $(mg/kg/day)^{-1}$ will be used.

$$RAD = \frac{\text{Risk Level}}{q1^*} = \frac{1 \times 10^{-5}}{1.1 \times 10^{-2}\ (mg/kg/d)^{-1}}$$

$$= 9.09 \times 10^{-4}\ mg/kg/d$$

Drinking Water Sources:

$$HNV = \frac{RAD \times BW}{WC_d + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{9.09 \times 10^{-4}\ mg/kg/d \times 70\ kg}{2\ l/d + [(0.0036 \times 7) + (0.0114 \times 12)]}$$

$$= 29\ ug/L$$

Non-Drinking Water Sources:

$$HNV = \frac{RAD \times BW}{WC_r + [(FC_{TL3} \times BAF_{TL3}) + (FC_{TL4} \times BAF_{TL4})]}$$

$$= \frac{9.09 \times 10^{-4}\ mg/kg/d \times 70\ kg}{0.01\ l/d + [(0.0036 \times 7) + (0.0114 \times 12)]}$$

$$= 3.7 \times 10^{2}\ ug/L$$

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