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Great Lakes Water Quality Initiative Criteria Documents for the Protection of Human Health

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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