Fact Sheet Date: March 12, 1998

NEW YORK STATE
- HUMAN HEALTH FACT SHEET -

Ambient Water Quality Value for Protection of Sources of Potable Water

SUBSTANCE: Chlorinated dibenzo-p-dioxins and Chlorinated dibenzofurans

CAS REGISTRY NUMBER: Not Applicable

AMBIENT WATER QUALITY VALUE: 7×10^{-7} ug/L equivalents of 2,3,7,8-tetrachlorodibenzo-p-dioxin*

Remarks: * Value is the total of the chlorinated dibenzo-p-dioxins and chlorinated dibenzofurans that are listed in the table below as equivalents of 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD). The 2,3,7,8-TCDD equivalent for a congener is obtained by multiplying the concentration of that congener by its toxicity equivalency factor (TEF) from the table below.

Human Health Toxicity Equivalency Factors (TEFs) for Individual Congeners

CONGENER	TEF
2,3,7,8-Tetrachlorodibenzo-p-dioxin	1
1,2,3,7,8-Pentachlorodibenzo-p-dioxin	0.5
1,2,3,4,7,8-Hexachlorodibenzo-p-dioxin	0.1
1,2,3,6,7,8-Hexachlorodibenzo-p-dioxin	0.1
1,2,3,7,8,9-Hexachlorodibenzo-p-dioxin	0.1
1,2,3,4,6,7,8-Heptachlorodibenzo-p-dioxin	0.01
Octachlorodibenzo-p-dioxin	0.001
2,3,7,8-Tetrachlorodibenzofuran	0.1
1,2,3,7,8-Pentachlorodibenzofuran	0.05
2,3,4,7,8-Pentachlorodibenzofuran	0.5
1,2,3,4,7,8-Hexachlorodibenzofuran	0.1
1,2,3,6,7,8-Hexachlorodibenzofuran	0.1
2,3,4,6,7,8-Hexachlorodibenzofuran	0.1
1,2,3,7,8,9-Hexachlorodibenzofuran	0.1
1,2,3,4,6,7,8-Heptachlorodibenzofuran	0.01
1,2,3,4,7,8,9-Heptachlorodibenzofuran	0.01
Octachlorodibenzofuran	0.001

BASIS: For 2,3,7,8-TCDD: Oncogenic
For all other congeners: Chemical Correlation and Oncogenic

I INTRODUCTION

The ambient water quality value applies to the water column and is designed to protect humans from the effects of contaminants in sources of drinking water; it is referred to as a Health (Water Source) or H(WS) value.

Regulations (6 NYCRR 702.2) require that the water quality value be based on the procedures in sections 702.3 through 702.7. Potential water quality values are derived below, and the value of 7×10^{-7} ug/L equivalents of 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD) is selected for the total of the chlorinated dibenzo-p-dioxins (CDDs) and chlorinated dibenzofurans (CDFs) as described under "Selection of Value."

II PRINCIPAL ORGANIC CONTAMINANT CLASSES AND SPECIFIC MCL (702.3)

A. Discussion

Both CDDs and CDFs do not have a Specific MCL as defined in 700.1. They are not in a principal organic contaminant class as defined in 700.1.

The U.S. Environmental Protection Agency has established a maximum contaminant level goal (MCLG) of zero ug/L and a MCL of 3×10^{-5} ug/L for drinking water for 2,3,7,8-TCDD. No MCLGs or MCLs have been established for other chlorinated dibenzo-p-dioxins or chlorinated dibenzofurans.

The New York State Department of Health does not have a Specific MCL for 2,3,7,8-TCDD or its congeners.

B. Derivation of Water Quality Value

Because CDDs and CDFs do not have a Specific MCL and are not in a principal organic contaminant class, no water quality value can be derived based on 702.3.

III ONCOGENIC EFFECTS OF 2,3,7,8-TCDD (702.4)

U.S. EPA (1995a) conducted a comprehensive evaluation of the oncogenic effects of 2,3,7,8-TCDD as part of its criteria development for the Great Lakes Water Quality Initiative (GLI). The GLI was a joint undertaking by U.S. EPA and the Great Lakes States and included representatives of interest groups. Its final regulations and the criteria document for this substance received extensive public review in a formal rulemaking process. U.S. EPA's documentation for their oncogenic criteria has been reviewed. The Department concludes that 2,3,7,8-TCDD is an oncogen under New York's definition in 6 NYCRR 700.1 and that U.S. EPA's toxicological basis is appropriate for derivation of a statewide value.

Exhibit I, excerpted from U.S. EPA (1995a), provides U.S. EPA's scientific basis for their criteria. These data will be used to calculate a water quality value for 2,3,7,8-TCDD for

protection from oncogenic effects using New York State procedures as described below.

U.S. EPA (1995a) selected the results of the Kociba et al. (1978) bioassay as the most appropriate dose-response data for deriving a water quality value. A summary of the data sets that demonstrated statistically and biologically significant increases in tumor response is presented in Exhibit I. U.S. EPA derived an oral cancer slope factor of 7.5×10^4 $[mg/(kg \cdot day)]^{-1}$ from female rat data in Kociba et al. (1978) with the liver tumor reevaluation of the Pathology Working Group (Sauer, 1990).

This slope factor was calculated by U.S. EPA using an interspecies scaling of doses based on the 2/3 power of relative body weights. Proposed New York State regulations call for such scaling to be done on the basis of the 3/4 power of relative body weights. An adjustment to U.S. EPA's slope is needed to account for the different scaling methods.

The adjustment factor for rat data (body weight of 0.35 kg) is a multiplication factor of 0.64, which results in a slope of 4.8×10^4 $[mg/(kg \cdot day)]^{-1}$.

The slope factor is converted to a human dose, at a lifetime risk level of one-in-one million as shown below.

$$\text{Human dose} = \frac{\text{risk}}{\text{slope}} = \frac{10^{-6}}{4.8 \times 10^4 \ [mg/(kg \cdot day)]^{-1}}$$

$$= 2.08 \times 10^{-11} \ mg/(kg \cdot day) = 2.08 \times 10^{-8} \ ug/(kg \cdot day)$$

The human dose above is converted to a potential water quality value based on a 70 kg adult consuming 2 liters of water per day as follows:

$$\text{Water Quality Value} = \frac{[2.08 \times 10^{-8} \ ug/(kg \cdot day)] \ [70 \ kg]}{[2 \ L/day]} = 7.28 \times 10^{-7} \ ug/L,$$

rounded to 7×10^{-7} ug/L

IV NON-ONCOGENIC EFFECTS OF 2,3,7,8-TCDD (702.5)

U.S. EPA (1995a) also conducted a comprehensive review of toxicological data on non-oncogenic effects for 2,3,7,8-TCDD as part of criteria development under GLI. The Department reviewed the toxicological basis for EPA's non-oncogenic criteria and concludes it is appropriate for the derivation of a statewide value. Exhibit II, excerpted from U.S. EPA (1995a), provides the scientific basis for their non-oncogenic criteria. These data will be used to develop a water quality value for 2,3,7,8-TCDD for protection from non-oncogenic effects using New York State procedures as described below.

U.S. EPA (1995a) selected the results of the study by Bowman et al. (1989) as the most appropriate for deriving a water quality value based on non-oncogenic effects. From these results they calculated an acceptable daily exposure (ADE)

of 1.3×10^{-9} mg/(kg · day), equivalent to an acceptable daily intake (ADI) developed under NYS procedures (702.5).

A potential water quality value is calculated from the ADI, above, based on a 70 kg adult consuming 2 liters of water per day and allocating 20% of the ADI to drinking water, as follows:

$$\text{Water Quality Value} = \frac{[1.3 \times 10^{-9} \text{ mg/(kg · day)}][1000 \text{ ug/mg}][70 \text{ kg}][0.2]}{[2 \text{ L/day}]} = 9 \times 10^{-6} \text{ ug/L}$$

V CHEMICAL CORRELATION (702.7)

A. 2,3,7,8-TCDD

A value based on chemical correlation is not applicable because data are sufficient to evaluate 2,3,7,8-TCDD based on sections 702.4 (oncogenic) and 702.5 (non-oncogenic).

B. Individual Congeners of CDDs and CDFs

U.S. EPA (1995b) promulgated toxicity equivalency factors for individual congeners of CDDs and CDFs as part of its criteria development for the Great Lakes Water Quality Initiative, based on a review of data contained in U.S. EPA (1989). The Department has reviewed these data and concludes that they are appropriate for derivation of toxicity equivalency factors for individual congeners on the basis of chemical correlation and comparative toxicity.

There are 209 congeners of 2,3,7,8-TCDD, which are structurally related to 2,3,7,8-TCDD and show similar kinds of toxic activity. The congeners vary structurally in degree of chlorination and degree of oxygenation, with dioxins having 2 oxygen atoms between chlorinated benzene rings and dibenzofurans having 1. A variety of toxic endpoints have been used to assess the degree of toxicity relative to 2,3,7,8-TCDD and the relative potencies show consistency from one endpoint to another. There is also a strong structure-activity relationship between structure and binding to the Ah receptor (Knutson and Poland, 1980).

There is a range of binding affinities for the Ah receptor with 2,3,7,8-TCDD showing maximum affinity and non-2,3,7,8-chlorine-substituted congeners showing minimum affinity (U.S. EPA, 1989). In a relative ranking scale, 2,3,7,8-TCDD is assigned a maximum value of 1 and the non-2,3,7,8-chlorine-substituted congeners a value of zero. The other 2,3,7,8-chlorine-substituted congeners demonstrated a range of significant affinities, but less than 2,3,7,8-TCDD.

In assigning TEFs, priority is generally given to the results from long-term, whole-animal studies, followed by results from short-term whole animal studies. Among the remaining short-term in-vivo and in-vitro data, priority is generally given to the results of enzyme induction studies. This is due to the fact that a good correlation has generally been observed between enzyme induction activity and short-term, whole-animal results; i.e., thymic atrophy ($r = 0.91$), bodyweight loss ($r = 0.84$) in rats, and inhibition of bodyweight gain in guinea pigs ($r = 0.93$) (NATO/CCMS, 1988).

The toxicological bases for the magnitudes of the TEFs for each individual or category of congeners are described below. U.S. EPA (1989) assigns a zero value to non-2,3,7,8-chlorine substituted dioxins and dibenzofurans and to mono-, di-, and tri-CDDs based on low affinity for the Ah receptor (Knutson and Poland, 1980). Based on the magnitude of mouse teratogenicity effects and observations on thymic atrophy and aryl hydrocarbon hydrolase (AHH) enzyme induction, 1,2,3,7,8-pentachloro-dibenzofuran is assigned a TEF of 0.05 and 2,3,4,7,8-pentachloro-dibenzofuran a TEF of 0.5. 2,3,7,8-Hexachlorodibenzo-p-dioxins and dibenzofurans are assigned a TEF of 0.1 based on the carcinogenic effects of these congeners in animals and in vivo short-term assays of thymic atrophy and AHH induction relative to 2,3,7,8-TCDD (U.S. EPA, 1989).

2,3,7,8-Heptachlorodibenzo-p-dioxins and dibenzofurans are assigned a TEF of 0.01 based on short-term in vitro results and the observations of Couture et al. (1988) that perchlorinated congeners slowly bioaccumulate in exposed animals. Highly chlorinated species such as heptachlorodibenzo-p-dioxins and dibenzofurans are likely to behave in a similar fashion (U.S. EPA, 1989).

Octachlorodibenzo-p-dioxin and dibenzofuran are assigned a TEF of 0.01 based on dioxin-like toxicity observed in animals exposed to these congeners for 13 weeks (Couture et al., 1988; U.S. EPA, 1989).

VI SELECTION OF VALUE

The H(WS) value is designed to protect humans from oncogenic and non-oncogenic effects from contaminants in sources of drinking water. To protect for these effects, regulations (6 NYCRR 702.2(b)) require that the value be the most stringent of the values derived using the procedures found in sections 702.3 through 702.7. The oncogenic value of 7×10^{-7} ug/L equivalents of 2,3,7,8-TCDD (6 NYCRR 702.4) is the most stringent value derived by these procedures and is the ambient water quality value for the total of the chlorinated dibenzo-p-dioxins and chlorinated dibenzofurans. The magnitude of chemical correlation based TEF values for the individual chlorinated dibenzo-p-dioxins and dibenzofurans (6 NYCRR 702.7) are the appropriate values assigned on the basis of similarity of functional groups and a review of toxicity.

VII REFERENCES

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6 NYCRR (New York State Codes, Rules and Regulations). Water Quality Regulations, Surface Water and Groundwater Classifications and Standards: Title 6 NYCRR, Chapter X, Parts 700-705. Albany, NY: New York State Department of Environmental Conservation.

10 NYCRR (New York State Codes, Rules and Regulations). Public Water Systems: Title 10 NYCRR, Chapter 1, State Sanitary Code, Subpart 5-1. Albany, NY: New York State Department of Health, Bureau of Public Water Supply Protection.

NATO/CCMS (North Atlantic Treaty Organization, Committee on the Challenges of Modern Society). 1988. Scientific basis for the development of international toxicity equivalency (I-TEF) factor method of risk assessment for complex mixtures of dioxins and related compounds. Report No. 178 (as cited in U.S. EPA, 1989).

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Initiative Criteria Documents for the Protection of Human Health. Washington, D.C.: Office of Water. EPA-820-B-95-006.

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New York State Department of Environmental Conservation
Division of Water
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EXHIBIT I
(From U.S. EPA, 1995a)

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 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.

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EXHIBIT II
(From U.S. EPA, 1995a)

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

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