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NEW YORK STATE
- HUMAN HEALTH FACT SHEET -

Ambient Water Quality Value for
Protection of Sources of Potable Water

SUBSTANCE: Di(2-ethylhexyl)adipate **CAS REGISTRY NUMBER:** 103-23-1

AMBIENT WATER QUALITY VALUE: 20 micrograms/liter (20 ug/L)

BASIS: Oncogenic Effects

INTRODUCTION

The physical, chemical, and toxicological properties of di(2-ethylhexyl)adipate have been reviewed (US EPA 1990, 1991, 1992, 1995). The following ambient water quality values were derived using these and other references and the procedures outlined in 6 NYCRR 702.2 through 702.7.

SPECIFIC MCL AND PRINCIPAL ORGANIC CONTAMINANT CLASS (702.3)

Di(2-ethylhexyl)adipate does not have a Specific MCL (maximum contaminant level) as defined in 6 NYCRR 700.1 and is not in a principal organic contaminant class as defined in 6 NYCRR 700.1. Therefore, a water quality value cannot be derived under 6 NYCRR 702.3.

ONCOGENIC EFFECTS (702.4)

Di(2-ethylhexyl)adipate induced liver tumors in mice in one chronic study, but was not oncogenic in rats under the conditions of a chronic study (NTP, 1981) and was not active in short-term tests indicative of potential oncogenic activity (US EPA, 1995). However, the hypothesized oncogenic mechanism for di(2-ethylhexyl)adipate (peroxisome proliferation) does not necessarily involve genotoxicity; thus, the lack of activity of di(2-ethylhexyl)adipate in short-term tests of oncogenic activity is not surprising.

Kluwe (1986) assessed the oncogenic potential of di(2-ethylhexyl)adipate and three other structurally similar compounds (di(2-ethylhexyl)phthalate, tris(2-ethylhexyl)phosphate, and sodium(2-ethylhexyl)sulfate) containing the 2-ethylhexyl moiety. One of these compounds (di(2-ethylhexyl)phthalate) is an oncogen under 6 NYCRR 700.1. The available data indicate that the mouse liver is a target organ for all four compounds; each compound induced hepatocellular tumors in mice. Only di(2-ethylhexyl)phthalate induced hepatocellular tumors in rats, even though the three other compounds were tested at higher doses than di(2-ethylhexyl)phthalate. These data suggest that the 2-ethylhexyl moiety may have a propensity for causing hepatocellular tumors in mice.

Given the above, di(2-ethylhexyl)adipate is an oncogen under 6 NYCRR 700.1 and the NTP (1981) study can be used to derive a water quality value based on oncogenic effects. The dose-response data for di(2-ethylhexyl)adipate were evaluated and a cancer potency factor of 0.0015 per milligram per kilogram per day (0.0015 $(mg/kg/day)^{-1}$) was derived using procedures consistent with those outlined in paragraphs (a) through (e) of 6 NYCRR 702.4. In the absence of sufficient scientific evidence to support the use of alternative procedures, the linearized multistage model (extra risk) and a cross-species scaling factor for carcinogen risk assessment based on the assumption that lifetime cancer risks are equal when daily administered doses are in proportion to body weights raised to the 3/4 power were used. The cancer potency factor was based on the most sensitive response in the most sensitive sex and species (the incidences of hepatocellular adenomas or carcinomas (3/50, 19/50, and 18/49) in female mice ingesting 0, 1,560, and 3,250 mg/kg/day, respectively, for two years), and an average body weight of 0.035 kg. The water concentration corresponding to the lower bound estimate on the dose associated with an excess lifetime human cancer risk of one-in-one million is 20 ug/L. This value was derived using the above cancer potency factor (0.0015 $(mg/kg/day)^{-1}$) and the procedure in paragraph (f) of 6 NYCRR 702.4.

In 1991, the U.S. EPA used the same tumor data and higher estimates of daily di(2-ethylhexyl)adipate intake by mice to calculate a cancer potency factor of 0.0012 $(mg/kg/day)^{-1}$ (US EPA, 1995), using procedures consistent with those outlined in paragraphs (a) through (e) of 6 NYCRR 702.4, including the use of the linearized multistage model. This cancer potency factor was calculated using a cross-species scaling factor for carcinogen risk assessment based on the assumption that lifetime cancer risks are equal when daily administered doses are in proportion to body weights raised to the 2/3 power (the surface area scaling factor). Proposed New York State regulations state that the scaling factor should be based on the assumption that lifetime cancer risks are equal when daily administered doses are in proportion to body weights raised to the 3/4 power. This change requires application of an adjustment factor to cancer potency factors calculated using a cross-species scaling factor based on surface area, and an adjusted cancer potency factor (0.00064 $(mg/kg/day)^{-1}$) was calculated by multiplying the US EPA cancer potency factor of 0.0012 $(mg/kg/day)^{-1}$ by 0.53 (the adjustment factor for a mouse body weight of 0.035 kg). This yields a value of 55 ug/L when the procedure in paragraph (f) of 6 NYCRR 702.4 is used. The US EPA estimated from the disappearance of food that the mice ate about 30% of their body weight in food each day, which is substantially higher

than the standard percentage (12 to 13%) used to estimate intake when experimental data are unavailable (Gold et al., 1984). The US EPA (1995) noted that there may have been spillage of the powdered food. Thus, the US EPA may have over-estimated food intake and under-estimated the cancer potency factor.

NON-ONCOGENIC EFFECTS (702.5)

Di(2-ethylhexyl)adipate causes changes in body and liver weight and is fetotoxic in laboratory animals (ICI, 1988a,b; US EPA, 1991, 1995). There are gaps in the toxicological data on the chronic and reproductive effects of di(2-ethylhexyl)adipate (US EPA, 1995). In 1991, the U.S. EPA used the available data to derive an oral reference dose (equivalent to an acceptable daily intake) of 600 micrograms per kilogram per day (600 ug/kg/day, rounded from the calculated value of 570 ug/kg/day) for di(2-ethylhexyl)adipate (Exhibit 1, taken from US EPA, 1995), using procedures consistent with those outlined in paragraphs (a) and (b) of 6 NYCRR 702.5. This reference dose was derived by application of a 300-fold uncertainty factor to a no-observed-effect level (NOEL) of 170 mg/kg/day for changes in body and liver weight and fetotoxicity observed in one-generation reproductive and teratology studies in rats (ICI, 1988a,b). A value of 4,200 ug/L is derived using the procedure outlined in paragraph (e) of 6 NYCRR 702.5 and allowing 20% of the acceptable daily intake (i.e., 600 ug/kg/day) to come from drinking water (6 NYCRR 702.5(c)).

However, the authors of the study identified the lowest dose in the study (28 mg/kg/day) as the clear-cut NOEL for fetotoxicity (ICI, 1988a). If an uncertainty factor of 100 is applied this dose, an oral reference dose (equivalent to an acceptable daily intake) of 280 ug/kg/day for di(2-ethylhexyl)adipate can be derived using procedures consistent with those outlined in paragraphs (a) and (b) of 6 NYCRR 702.5. An uncertainty factor of 100 was used to account for human variability, differences between animals and humans and the nature and severity of the observed effects. A value of 1,960 ug/L is derived using the procedure outlined in paragraph (e) of 6 NYCRR 702.5 and allowing 20% of the acceptable daily intake to come from drinking water (6 NYCRR 702.5(c)).

CHEMICAL CORRELATION (702.7)

A value based on chemical correlation was not derived because there were sufficient data to derive values based on oncogenic effects (6 NYCRR 702.4) and non-oncogenic effects (6 NYCRR 702.5).

OTHER STANDARDS AND GUIDELINES

Under New York State Department of Health regulations for drinking-water standards (10 NYCRR Part 5), di(2-ethylhexyl)adipate is an unspecified organic contaminant (UOC) and has a MCL of 50 ug/L. Under the Safe Drinking Water Act, the federal maximum contaminant level goal (MCLG) and the MCL for di(2-ethylhexyl)adipate are both 400 ug/L (rounded from the calculated value of 420 ug/L), assuming a 70-kg adult drinks 2 L/day, allocating 20% of the U.S. EPA reference dose (600 ug/kg/day) to drinking water and applying an additional uncertainty factor of 10 for possible oncogenic effects (US EPA, 1992). The World Health Organization (WHO) derived a guideline value of 80 ug/L for di(2-ethylhexyl)adipate in drinking water (rounded from 84 ug/L), assuming a 60-kg adult drinks 2 L/day and allocating 1% of the WHO reference dose (280 ug/kg/day) to drinking water (WHO, 1993).

SELECTION OF VALUE

According to 6 NYCRR 702.2(b), the selected ambient water quality value shall be the most stringent of the values derived using the procedures found in 6 NYCRR 702.3 through 702.7. This value is 20 ug/L (based on oncogenic effects) and is the value selected as the water quality value for di(2-ethylhexyl)adipate.

REFERENCES

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SEARCH STRATEGY: ON-LINE TOXICOLOGIC DATABASE

Toxline (1981 to March, 1995) was searched linking the CAS Registry Number of di(2-ethylhexyl)adipate with the keyword "toxicity."

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